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REPORT OF THE ADVISORY COMMITTEE ON THE
BIOLOGICAL EFFECTS OF IONIZING RADIATIONS

DIVISION OF MEDICAL SCIENCES

NATIONAL ACADEMY OF SCIENCES • NATIONAL RESEARCH COUNCIL
WASHINGTON, D.C. 20006

NOVEMBER 1972

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NOTICE

The study reported herein was undertaken under the aegis of the National Research Council with the express approval of the Governing Board of the NRC. Such approval indicated that the Board considered that the problem is of national significance, that elucidation or solution of the problem required scientific or technical competence, and that the resources of the NRC were particularly suitable to the conduct of the project. The institutional responsibilities of the NRC were then discharged in the following manner:

The members of the study committee were selected for their individual scholarly competence and judgment with due consideration for the balance and breadth of disciplines. Responsibility for all aspects of this report rests with the study committee, to whom we express our sincere appreciation.

Although the reports of our study committees are not submitted for approval to the Academy membership nor to the Council, each report is reviewed by a second group of appropriately qualified persons according to procedures established and monitored by the Academy's Report Review Committee. Such reviews are intended to determine, inter alia, whether the major questions and relevant points of view have been addressed and whether the reported findings, conclusions, and recommendations arose from the available data and information. Distribution of the report is approved, by the President, only after satisfactory completion of this review process.

FOREWORD

In the summer of 1970, the Federal Radiation Council (whose activities have since been transferred to the Radiation Office of the EPA) asked the National Academy of Sciences for information relevant to an evaluation of present radiation protection guides. This report is in response to that request.

It presents a summary and analysis, by members of the Advisory Committee on the Biological Effects of Ionizing Radiations and its subcommittees, of current knowledge relating to risks from exposure to ionizing radiation. In many respects, the report is a sequel to the reports of the Committee on the Biological Effects of Atomic Radiation, published by the NAS-NRC from 1956 to 1961.

We extend our gratitude to the members of the committees and their consultants who contributed to the development of this report, many of whom have given unstintingly of their time and thought to this effort. We hope that the information contained herein will serve not only as a summary of present knowledge on the effects of ionizing radiation on human populations but also as a scientific basis for the development of suitable radiation protection standards.

We also wish to thank Dr. Cavalli-Svorza, Dr. William Cole, Dr. Maurice Fox, Mr. Joseph Gitlin, Dr. Ralph Lapp, Dr. Joshua Lederberg, Dr. Peter Morris, Mr. Lester Rogers, Dr. Francisco Sella, Dr. Charlotte Silverman, Dr. Alice Stewart, Dr. Lauriston Taylor, Dr. John C. Thompson, and Mrs. Edythalena Tompkins, all of whom gave of their time to meet with various subcommittees.

Preface

This report of the National Academy of Sciences - National Research Council Advisory Committee on the Biological Effects of Ionizing Radiations (BEIR Committee) deals with the scientific basis for the establishment of radiation protection standards and encompasses a review and re-evaluation of existing scientific knowledge concerning radiation exposure of human populations. The present basis of radiation protection is essentially the establishment of single upper limits for individual and population average exposures with the understanding that any biological risks should be offset by commensurate benefits and that these risks should be kept as low as practicable. It has become apparent that these current concepts of radiation protection may not be adequate in a future age of large-scale use of nuclear energy. Inadequacy arises because there is the potential for radiation exposure of entire populations and such exposure may be an alternative to other types of hazards as, for example, the substitution of radioactive contaminants from nuclear power plants for the combustion products from fossil fuel plants. Thus there is a need somehow to make comparisons of biological risks and benefits not only for radiation but for the alternative options. In this report it has not been possible for us to deal with critical interacting factors such as socio-economics, energy needs, and comparative effects of other toxicological agents; nor have we attempted to explore in detail technological matters such as sustained engineering performance of power reactors, large-scale waste disposal, or the problem of catastrophic accidents. Nevertheless, we have felt it urgent to call attention to these issues because ultimately, decisions will have to be made involving them, and public acceptance gained on the basis of providing society with the services that it needs at a minimum risk to health and the environment.

The BEIR Committee has endeavored to ensure that no sources of relevant knowledge or expertise were overlooked in its study and toward this end has established and maintained liaison with appropriate national and international organizations, and has solicited the opinions and counsel of individual scientists. The Committee wishes to express appreciation to those who served on the Subcommittees, and to the many organizations and individuals who have cooperated by providing viewpoints and information. The members of the Committee and Subcommittees acted as individuals, not as representatives of their organizations.

Chapters IV through VII represent the reports of the respective Subcommittees but may have been modified by the Committee. All members of the Committee approve the substance of the report if not necessarily each specific detail.

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CONTENTS

Page

Foreword ... i
Preface ... iii
Members of the Advisory Committee on the Biological Effects of Ionizing Radiation ... v
Summary and Recommendations ... 1
Chapter I Introduction ... 5
Chapter II Needs of the Times ... 7
Chapter III Sources of Ionizing Radiation and Population Exposures ... 11
Chapter IV Environmental Transport and Effects of Radionuclides ... 21
Chapter V Genetic Effects of Ionizing Radiation ... 41
Chapter VI Effects of Ionizing Radiation on Growth and Development ... 73
Chapter VII Somatic Effects of Ionizing Radiation ... 83

Appendices

A. General Bibliography ... 201
B. Glossary ... 213
C. Record of Meetings ... 217

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TABLES AND FIGURES

Page

Chapters I and II

None

Chapter III

Estimated Total Annual Average Doses from Natural Radiation in the United States (Whole-body) Table 1 12
Summary of Estimates of Annual Whole-body Dose Rates in the United States (1970) Table 2 19

Chapter IV

None

Chapter V

Sources of Genetically Significant Radiation Table 1 50
Estimated Effects of Radiation for Specific Genetic Damage Table 2 54
Estimates of Cytogenetic Effects from 5 Rem per Generation Table 3 55
Estimated Effect of 5 Rem per Generation on a Population of One Million Table 4 57

Chapter VI

Children with Small Head Circumference Following *In Utero* Exposure to the Hiroshima Bomb Table 1 75

Chapter VII

Appendix I—Bases of Evaluation of Risks of Low-level Radiation

Hypothetical Dose-effect Curves Fig. 1 98

Appendix IIa—Leukemia

Incidence of Leukemia in A-Bomb Survivors, by T-65 Dose and by City, 1950-1966 Table a-1 102
Incidence of Leukemia in A-bomb Survivors by T-65 Dose, City, and Type of Leukemia, 1950-1966 Table a-2 105
Approximate Factors for Estimating Excess Cases of Leukemia, Based on the Experience of the A-bomb Survivors, 1950-1966 Table a-3 107
Mortality from Leukemia in A-bomb Survivors, by T-65 Dose and by City, 1950-1970 Table a-4 108
Calculation of Excess Deaths from Leukemia, 1950-1970, by Age ATB and City Table a-5 109
Observed and Expected Deaths from Leukemia, 1935-1960, Among 14,554 Patients with Ankylosing Spondylitis Treated by X-ray, 1935-1955 Table a-6 110
Risk Estimates for Leukemia Table a-7 117
Annual Incidence Rate of Definite and Probable Leukemia per 100,000 Population of A-bomb Survivors Fig. a-1 104
Definite and Probable Leukemia in the ABCC Master Sample by T-65 RBE Dose, 1950-1966 Fig. a-2 104
Myeloid Leukemia in Male Mice Fig. a-3 115

Preceding page blank

Page

Appendix IIb—Thyroid

Basis of Risk Estimates for Thyroid Cancer, Childhood Exposure .... Table b-1 124
Incidence of Thyroid Neoplasms versus Thyroid Dose (rads) .... Fig. b-1 121
Incidence of Thyroid Nodularity in Relation to Estimated Cumulative Dose to the Thyroid Gland .... Fig. b-2 121

Appendix IIc—Bone

Summary of Risk Estimates for Bone Cancer .. Summary 123
Basis of Risk Estimates for Bone Cancer .... Table c-1 129
Risk of Bone Cancer, Radium-226 Exposed Group "Dial Painters"; Followup through 1971 .... Fig. c-1 130
Risk of Bone Cancer, Radium-224 Exposed German Patients, Followup through 1969 ..... Fig. c-2 131

Appendix IId—Skin

Relative Risks for Skin Cancer at Various Exposure Levels after Therapeutic Radiation Table d-1 134

Appendix IIe—Breast

Basis of Risk Estimates for Breast Cancer ..... Table e-1 139
Follow-up Details of the 306 Non-fluoroscoped and the 243 Fluoroscoped Patients who Survived at Least 10 Years .... Table e-2 142
Incidence of Breast Cancers from Fluoroscopies .... Fig. e-1 138
Mortality Ratio for Breast Cancer vs. Age ATB Fig. e-2 140

Appendix IIf—Lung

Summary of Risk Estimates for Bronchial Cancer .... Summary 150
Basis of Risk Estimates for Lung Cancer .... Table f-1,2 151
Risk of Lung Cancer, Hiroshima-Nagasaki Survivors, 1955-1971 .... Fig. f-1 153
Risk of Lung Cancer, U. S. Uranium Miners 1951-1971 .... Fig. f-2 154
Risk of Lung Cancer, Newfoundland Fluorspar Miners, 1952-1968 .... Fig. f-3 155

Appendix IIg—Other Neoplasms

Basis of Risk Estimates for Stomach Cancer .. Table g-1 158
Basis of Risk Estimates for all G. I. Cancer except Stomach .... Table g-2 159

Appendix IIh—All Cancers Other than Leukemia

Basis of Risk Estimates for All Cancer except Leukemia .... Table h-1 161
Table h-2 162

Appendix II A 2—Cancer following Irradiation before Conception or during Intrauterine Life

Basis of Risk Estimates for Leukemia, and for All Cancers except Leukemia, after Fetal Radiation .... Table 2-1 163

Appendix II A 3—Total Cancer Risk

Page
Calculation of the Excess Annual Number of Cancer Deaths for Individuals Exposed from 20 to 65 years of Age .... Summary 170
Estimated Numbers of Deaths per Year in the U.S. Population Attributable to Continual Exposure at a Rate of 0.1 rem per Year, Based on Mortality from Leukemia and From all Other Malignancies Combined .... Table 3-1 169
Assumed Values Used in Calculating Estimates of Risk Shown in Table 3-1 .... Table 3-2 171
Calculation of the Annual Number of Excess Cancer Deaths in the U. S. Population from Continuous Exposure to 0.1 rem/year, Using Relative Risk Model .... Table 3-3 172
Calculations of Annual Number of Excess Cancer Deaths in the U. S. Population from Continuous Exposure to 0.1 rem/year, Using the Absolute Risk Model .... Table 3-4 173

Appendix II B—Mortality from Causes of Death Other than Cancer
None

Appendix II C—Morbidity from Causes Other Than Cancer
None

Appendix III—Analysis of Viewpoints on Record Variation in Cancer Induction per rad .... Table III-I 183
A Comparison of Relative and Absolute Risk Estimates of the Major Types of Malignancies Induced Among the A-bomb Survivors (all Ages) .... Table III-2 185
The Relative Risk of Induction of all Malignancies (except Leukemia) in the A-bomb Survivors, Versus Age ATB .... Fig. III-1 184
The Absolute Risk of Induction of all Malignancies (except leukemia) in the A-bomb Survivors Versus Age ATB .... Fig. III-2 187

Appendix IV—Calculation of Confidence Limits
None

Appendix V—Radiation Dosimetry of Heavily Irradiated Sites in Patients Treated for Ankylosing Spondylitis

Stomach Types .... Fig. V-1 191
Transverse Section of Cadaver, at Thoracic-12 Fig. V-2 193
Lung Diagram .... Fig. V-3 194

Appendix VI—Definitions and Notes
None

SUMMARY AND RECOMMENDATIONS

In anticipation of the widespread increased use of nuclear energy, it is time to think anew about radiation protection. We need standards for the major categories of radiation exposure, based insofar as possible on risk estimates and on cost-benefit analyses which compare the activity involving radiation with the alternative options. Such analyses, crude though they must be at this time, are needed to provide a better public understanding of the issues and a sound basis for decision. These analyses should seek to clarify such matters as: (a) the environmental and biological risks of given developments, (b) a comparison of these risks with the benefits to be gained, (c) the feasibility and worth of reducing these environmental and biological risks, (d) the net benefit to society of a given development as compared to the alternative options.

In the foreseeable future, the major contributors to radiation exposure of the population will continue to be natural background with an average whole-body dose of about 100 mrem/year, and medical applications which now contribute comparable exposures to various tissues of the body. Medical exposures are not under control or guidance by regulation or law at present. The use of ionizing radiation in medicine is of tremendous value but it is essential to reduce exposures since this can be accomplished without loss of benefit and at relatively low cost. The aim is not only to reduce the radiation exposure to the individual but also to have procedures carried out with maximum efficiency so that there can be a continuing increase in medical benefits accompanied by a minimum radiation exposure.

Concern about the nuclear power industry arises because of its potential magnitude and widespread distribution. Based on experience to date and present engineering judgment, the contribution to radiation exposure averaged over the U. S. population from the developing nuclear power industry can remain less than about 1 mrem per year (about 1% of natural background) and the exposure of any individual kept to a small fraction of background provided that there is: (a) attainment and long-term maintenance of anticipated engineering performance, (b) adequate management of radioactive wastes, (c) control of sabotage and diversion of fissionable material, (d) avoidance of catastrophic accidents.

The present Radiation Protection Guide for the general population was based on genetic considerations and conforms to the BEAR Committee recommendations that the average individual exposure be less than 10 R (Roentgens) before the mean age of reproduction (30 years). The FRC did not include medical radiation in its limits and set 5 rem as the 30-year limit (0.17 rem per year).

Present estimates of genetic risk are expressed in four ways: (a) *Risk Relative to Natural Background Radiation.* Exposure to man-made radiation below the level of background radiation will produce additional effects that are less in quantity and no different in kind from those which man has experienced and has been able to tolerate throughout his history. (b) *Risk Estimates for Specific Genetic Conditions.* The expected effect of radiation can be compared with current incidence of genetic effects by use of the concept of doubling dose (the dose required to produce a number of mutations equal to those which occur naturally). Based mainly on experimental studies in the mouse and *Drosophila* and with some support from observations of human populations in Hiroshima and Nagasaki, the doubling dose for chronic radiation in man is estimated to fall in the range of 20-200 rem. It is calculated that the effect of 170 mrem per year (or 5 rem per 30-year reproduction generation) would cause in the first generation between 100 and 1800 cases of serious, dominant or X-linked diseases and defects per year (assuming 3.6 million births annually in the U.S.). This is an incidence of 0.05%. At equilibrium (approached after several generations) these numbers would

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be about five-fold larger. Added to these would be a smaller number caused by chromosomal defects and recessive diseases. (c) *Risk Relative to Current Prevalence of Serious Disabilities.* In addition to those in (b) caused by single-gene defects and chromosome aberrations are congenital abnormalities and constitutional diseases which are partly genetic. It is estimated that the *total* incidence from all these including those in (b) above, would be between 1100 and 27,000 per year at equilibrium (again, based on 3.6 million births). This would be about 0.75% at equilibrium, or 0.1% in the first generation. (d) *The Risk in Terms of Overall Ill-Health.* The most tangible measure of total genetic damage is probably "ill-health" which includes but is not limited to the above categories. It is thought that between 5% and 50% of ill-health is proportional to the mutation rate. Using a value of 20% and a doubling dose of 20 rem, we can calculate that 5 rem per generation would eventually lead to an increase of 5% in the ill-health of the population. Using estimates of the financial costs of ill-health, such effects can be measured in dollars if this is needed for cost-benefit analysis.

Until recently, it has been taken for granted that genetic risks from exposure of populations to ionizing radiation near background levels were of much greater import than were somatic risks. However, this assumption can no longer be made if linear non-threshold relationships are accepted as a basis for estimating cancer risks. Based on knowledge of mechanisms (admittedly incomplete) it must be stated that tumor induction as a result of radiation injury to one or a few cells of the body cannot be excluded. Risk estimates have been made based on this premise and using linear extrapolation from the data from the A-bomb survivors of Hiroshima and Nagasaki, from certain groups of patients irradiated therapeutically, and from groups occupationally exposed. Such calculations based on these data from irradiated humans lead to the prediction that additional exposure of the U. S. population of 5 rem per 30 years could cause from roughly 3,000 to 15,000 cancer deaths annually, depending on the assumptions used in the calculations. The Committee considers the most likely estimate to be approximately 6,000 cancer deaths annually, an increase of about 2% in the spontaneous cancer death rate which is an increase of about 0.3% in the overall death rate from all causes.

Given the estimates for genetic and somatic risk, the question arises as to how this information can be used as a basis for radiation protection guidance. Logically the guidance or standards should be related to risk. Whether we regard a risk as acceptable or not depends on how avoidable it is, and, to the extent not avoidable, how it compares with the risks of alternative options and those normally accepted by society.

There is reason to expect that over the next few decades, the dose commitments for all man-made sources of radiation except medical should not exceed more than a few millirems average annual dose to the entire U. S. population. The present guides of 170 mrem/yr grew out of an effort to balance societal needs against genetic risks. It appears that these needs can be met with far lower average exposures and lower genetic and somatic risk than permitted by the current Radiation Protection Guide. To this extent, the current Guide is unnecessarily high.

The exposures from medical and dental uses should be subject to the same rationale. To the extent that such exposures can be reduced without impairing benefits, they are also unnecessarily high.

It is not within the scope of this Committee to propose numerical limits of radiation exposure. It is apparent that sound decisions require technical, economic and sociological considerations of a complex nature. However, we can state some general principles, many of which are well-recognized and in use, and some of which may represent a departure from present practice.

a) No exposure to ionizing radiation should be permitted without the expectation of a commensurate benefit.

b) The public must be protected from radiation but not to the extent that the degree of protection provided results in the substitution of a worse hazard for the radiation avoided. Additionally there should not be attempted the reduction of small risks even further at the cost of large sums of money that spent otherwise, would clearly produce greater benefi

c) There should be an upper limit of man-made non-medical exposure for individuals in the general population such that the risk of serious injury from somatic effects in such individuals is very small relative to risks that are normally accepted. Exceptions to this limit in specific cases should be allowable only if it can be demonstrated that meeting it would cause individuals to be exposed to other risks greater than those from the radiation avoided.

d) There should be an upper limit of man-made non-medical exposure for the general population. The average exposure permitted for the population should be considerably lower than the upper limit permitted for individuals.

e) Medical radiation exposure can and should be reduced considerably by limiting its use to clinically indicated procedures utilizing efficient exposure techniques and optimal operation of radiation equipment. Consideration should be given to the following:

   1) Restriction of the use of radiation for public health survey purposes, unless there is a reasonable probability of significant detection of disease.

   2) Inspection and licensing of radiation and ancillary equipment.

   3) Appropriate training and certification of involved personnel. Gonad shielding (especially shielding the testis) is strongly recommended as a simple and highly efficient way to reduce the Genetically Significant Dose.

f) Guidance for the nuclear power industry should be established on the basis of cost-benefit analysis, particularly taking into account the total biological and environmental risks of the various options available and the cost-effectiveness of reducing these risks. The quantifying of the "as low as practicable" concept and consideration of the net effect on the welfare of society should be encouraged.

g) In addition to normal operating conditions in the nuclear power industry, careful consideration should be given to the probabilities and estimated effects of uncontrolled releases. It has been estimated that a catastrophic accident leading to melting of the core of a large nuclear reactor could result in mortality comparable to that of a severe natural disaster. Hence extraordinary efforts to minimize this risk are clearly called for.

h) Occupational and emergency exposure limits have not been specifically considered but should be based on those sections of the report relating to somatic risk to the individual.

i) In regard to possible effects of radiation on the environment, it is felt that if the guidelines and standards are accepted as adequate for man then it is highly unlikely that populations of other living organisms would be perceptibly harmed. Nevertheless, ecological studies should be improved and strengthened and programs put in force to answer the following questions about release of radioactivity to the environment: (1) how much, where, and what type of radioactivity is released; (2) how are these materials moved through the environment; (3) where are they concentrated in natural systems; (4) how long might it take for them to move through these systems to a position of contact with man; (5) what is their effect on the environment itself; (6) how can this information be used as an early warning system to prevent potential problems from developing?

j) Every effort should be made to assure accurate estimates and predictions of radiation equivalent dosages from all existing and planned sources. This requires use of present knowledge on transport in the environment, on metabolism, and on relative biological efficiencies of radiation as well as further research on many aspects.

Chapter I

INTRODUCTION

The potential effects of ionizing radiation on human populations have been a concern of the scientific community for several decades. The oldest of the scientific bodies now having responsibility in this area are the International Commission on Radiological Protection (ICRP), formed in 1928, and the National Council on Radiation Protection and Measurements (NCRP), a United States organization initially formed in 1929 as the Advisory Committee on X-ray and Radium Protection. Both have maintained continuing studies of radiation protection problems that are of special relevance to the work of this Committee.

In the 1940's with the establishment of the U.S. Atomic Energy Commission and its program, there was recognition of possible radiation problems and large-scale animal experiments were initiated. In the early 1950's, as a result of the testing of nuclear weapons, public concern arose about the potential effects of ionizing radiation on human populations. In 1955, as a response to this concern, the President of the National Academy of Sciences (NAS) appointed a group of scientists to conduct a continuing appraisal of the effects of atomic radiation on living organisms. That study, entitled "Biological Effects of Atomic Radiation," was supported by funds from the Rockefeller Foundation and led to a series of reports by six committees issued from 1956-1963 and which are generally referred to as the BEAR reports.

Also, in 1955, the General Assembly of the United Nations established the UN Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), which, among other tasks associated with monitoring and assembling reports of radiation exposure throughout the world, was "to make yearly progress reports and to develop a summary of reports received on radiation levels and radiation effects on man and his environment. . . ." (UNSCEAR 1969). The periodic reports issued by UNSCEAR (the latest in 1969), in accordance with its objective, have served as a review of worldwide scientific information and opinion concerning human exposure to atomic radiation.

In 1959, the Federal Radiation Council (FRC) was formed to provide a federal policy on human radiation exposure. A major function of the FRC was to "advise the President with respect to radiation matters, directly or indirectly affecting health, including guidance for all Federal agencies in the formulation of radiation standards and in the establishment and execution of programs of cooperation with States. . . . ." The FRC published eight reports, the latest in 1967.

In 1964, at the request of the FRC, the National Academy of Sciences - National Research Council (NAS-NRC) established an Advisory Committee to the Federal Radiation Council within the Division of Medical Sciences of NRC. The Advisory Committee has continued to review and evaluate available scientific evidence bearing on a variety of problems of radiation exposure and protection and to issue reports of its deliberations.

The BEAR reports led to a basis for public understanding of the expected effects of the testing of nuclear devices that had occurred to that date and introduced the important concept of regulation of average population doses on the basis of genetic risk to future generations. These reports also emphasized medical-dental x-rays as the greatest source of man-made radiation exposure of the population. However, in the late 1960's, concern arose that developing peacetime applications of nuclear energy, particularly the growth of a nuclear power industry for production of electricity, could cause serious exposure of the human population to

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radiation. Thus, in February 1970, the FRC asked the NAS-NRC Advisory Committee to consider a complete review and re-evaluation of the existing scientific knowledge concerning radiation exposure to human populations. This request from the FRC came about because of: (1) a naturally developing sequence of the Advisory Committee's concern that there had been no detailed overall review since the BEAR reports; (2) new factors that might need to be considered, such as optional methods of producing electrical energy and types of environmental contamination different from those previously encountered; and (3) a growing number of allegations made in the public media and before Congressional committees that the existing radiation protection guides were inadequate and could lead to serious hazard to the health of the general population.

The NAS-NRC Advisory Committee, on 25 March 1970, accepted the task proposed by the FRC and subsequently enlarged its membership accordingly. On 2 October 1970, the Environmental Protection Agency (EPA) was established by the President's Reorganization Plan No. 3 of 1970. On 2 December 1970 the activities and functions of the FRC were transferred to the Radiation Office of the EPA. Because the FRC had ceased to exist as a specific body, the NAS-NRC Advisory Committee requested a change in its title. The President of the NAS renamed the Committee, the Advisory Committee on the Biological Effects of Ionizing Radiations (BEIR); functions, activities, membership, and staffing were not changed.

The task accepted in principle by the NAS-NRC Advisory Committee on 25 March 1970 is specified below in detail as a part of the contract agreement between NAS and the Department of Health, Education, and Welfare signed 1 September 1970.

"Independently and not as an agent of the Government, the Contractor shall furnish to the Department of Health, Education, and Welfare, for the Federal Radiation Council, consultation and advisory services on the evaluation and interpretation of scientific problems pertaining to the biological effects of ionizing radiation. In performing the work and services provided for herein the Contractor shall:

1. Review the scientific bases used for the evaluation of risks at low levels of exposure to ionizing radiations (Chapters III-VII)
2. Select the scientific basis it recommends the FRC use. (pp. 3-9)
3. Make such estimates of risk as it deems scientifically appropriate. (Genetic, Tables 2, 3, 4; G & D, pp. 79-80, Somatic, pp. 89-90)
4. Clearly delineate the interpretations and meaning that can be attributed to the estimates of risks when they are made. (pp. 1-3)
5. Consider a broad spectrum of exposure conditions and biological effects, including:
   a) exposure conditions relevant to the general public, (Entire report)
   b) exposure conditions relevant to the radiation workers, (p. 171)
   c) somatic risk evaluation, (Chapter VII)
   d) genetic risk evaluation, (Chapter V)
   e) teratogenic effects, (Chapter VI)
   f) effects on the environment as may affect man. (Chapter IV)
6. Utilize the services of experts drawn from appropriate fields of science, technology, and other professional competences selected on the basis of the Contractor's judgement of professional competence and scientific objectivity."

To carry out the required review and analysis, five subcommittees were formed to deal with the following subject areas: (1) general considerations, especially societal interactions, (2) environmental effects, (3) genetic effects, (4) somatic effects, (5) effects on growth and development.

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*Parenthetical references are to sections of this report particularly relevant to these points

Chapter II

NEEDS OF THE TIMES

A. Quantification of Risk

Deleterious effects in individuals and populations of living organisms cannot be attributed to exposure to ionizing radiation at levels near that of average natural background except by inference. Such effects are not directly observable. It has been taken for granted by many that exposure to additional radiation near background levels, and especially within variations of natural background, represents a risk so small compared with other hazards of life that any associated non-trivial benefit would far offset any harm caused. The effects of such radiation exposures have been variously regarded as insignificant, negligible, tolerable, permissable, acceptable. But if in fact any level of radiation will cause some harm (no threshold), and if in fact entire populations of nations or of the world are exposed to additional man-made radiation, then, for decisions about radiation protection, it becomes necessary to quantify the risks; that is, to estimate the probabilities or frequencies of effects.

Such estimates, as discussed later, are fraught with uncertainty. However, they are needed as a basis for logical decision-making and may serve to stimulate the gaining of data for assessment of comparative hazards from technological options and development, at the same time promoting better public understanding of the issues.

B. Cost-Benefit Analysis

When the risk from radiation exposure from a given technological development has been estimated, it is then logical for the decision-making process that comparisons be made and consideration given to (a) benefits to be attained, (b) costs of reducing the risks, or (c) risks of the alternative options including abandonment of the development. The concept of always balancing the risk of radiation exposure against the expected benefit has been well-recognized and accepted, but no serious attempt has been made to evaluate both sides of the equation in any way that could lead to operational guidance. Official recommendations call for radiation exposure to be kept at a level "as low as practicable," a policy that emphasizes and encourages sound practice. However, risk-estimates and cost-benefit analysis are needed for decision-making. An additional important point, often overlooked, is that even if the benefit outweighs the biological cost, it is in the public interest that the latter must still be reduced to the extent possible providing the health gains achieved per unit of expenditure are compatible with the cost-effectiveness of other societal efforts.

It appears logical to attempt to express both risks and benefits in comparable terms - dollars. To a limited degree risks can be estimated in such terms. For example, the statement of risk can be expressed in terms of cost to an individual or to his family and society since there are specific expenses attributable to an effect. Similarly, estimates can be made of expenses required to effect given reductions of exposure to harmful agents. In some instances, it may not be necessary to use absolute dollar costs: that is, one can compare the cost of different ways of producing the same desired objective. Given the need for additional electrical power, one might compare nuclear plants and fossil fuel plants directly in terms of total biological and environmental costs per unit of electricity produced. Often however, there will be need for information on absolute costs. This will occur when decisions have to be made on whether the public interest is better served by spending our limited resources on health gains from reducing contamination or by spending for other societal needs.

It must be emphasized that there are many inherent problems in cost-benefit analysis that will prevent rigorous application in the very complex systems of present concern to society. These include the implication of assigning a monetary value to human life, suffering or productivity; the difficulty in assessment of factors related to the quality of life such as recreational water and land resources; the fact that the costs and benefits may not accrue to the same members of the population, or even to the same generation; and the virtual impossibility of establishing a single cost system that would be socially acceptable and still take into account differences in individual willingness to accept various types of risks. An illustration of the latter points is the observation that health and environmental effects from power plants would be reduced by their location in relatively unpopulated areas. Yet the people in such areas generally are not the ones who need the additional electrical energy.

Despite these uncertainties, there are important advantages in attempting cost-benefit analyses. There is a focus on the biological and environmental cost from technological developments and the need for specific information becomes apparent. Thus, for example, we find relatively little data available on the health risks of effluents from the combustion of fossil fuels. Furthermore, it is becoming increasingly important that society not expend enormously large resources to reduce very small risks still further, at the expense of greater risks that go unattended; such imbalances may pass unnoticed unless a cost-benefit analysis is attempted. If these matters are not explored, the decisions will still be made and the complex issues resolved either arbitrarily or by default since the setting and implementation of standards represent such a resolution.

C. Standards

The present radiation standards used by the Federal Government are based on the recommendations of the Federal Radiation Council (FRC). The FRC developed the Radiation Protection Guide that is defined as "the radiation dose which should not be exceeded without careful consideration of the reasons for doing so; every effort should be made to encourage the maintenance of radiation doses as far below this guide as practicable." The FRC also indicated that "there should not be any man-made radiation exposure without the expectation of benefit resulting from such exposure."

The present status of Radiation Protection Guides for the general population is presented as direct quotation from FRC Report No. 1 (italics added).

> 5.2 We believe that the current population exposure resulting from background radiation is a most important starting point in the establishment of Radiation Protection Guides for the general population. This exposure has been present throughout the history of mankind, and the human race has demonstrated an ability to survive in spite of any deleterious effects that may result. Radiation exposures received by different individuals as a result of natural background are subject to appreciable variation. Yet, any differences in effects that may result have not been sufficiently great to lead to attempts to control background radiation or to select our environment with background radiation in mind.
>
> 5.3 On this basis, and after giving due consideration to the other bases for the establishment of Radiation Protection Guides, it is our basic recommendation that the *yearly radiation exposure to the whole body of individuals in the general population (exclusive of natural background and the deliberate exposure of patients by practitioners of the healing arts) should not exceed 0.5 rem.* We note the essential agreement between this value and current recommendations of the ICRP and NCRP. It is not reasonable to establish Radiation Protection Guides for the population which take into account all possible combinations of circumstances. Every reasonable effort should be made to keep exposures as far below this level as practicable. Similarly, it is obviously appropriate to exceed this level if a careful study indicates that the probable benefits will outweigh the potential risk. Thus, the degree of control effort does not depend solely on whether or not this Guide is being exceeded. Rather, any

exposure of the population may call for some control effort, the magnitude of which increases with the dose.

5.4 Under certain conditions, such as widespread radioactive contamination of the environment, the only data available may be related to average contamination or exposure levels. Under these circumstances, it is necessary to make assumptions concerning the relationship between average and maximum doses. The Federal Radiation Council suggests the use of the arbitrary assumption that the majority of individuals do not vary from the average by a factor greater than three. *Thus, we recommend the use of 0.17 rem for yearly whole-body exposure of average population groups.* (It is noted that this guide is also in essential agreement with current recommendations of the NCRP and the ICRP.) It is critical that this guide be applied with reason and judgment. Especially, it is noted that the use of the average figure, as a substitute for evidence concerning the dose to individuals, is permissible only when there is a probability of appreciable homogeneity concerning the distribution of the dose within the population included in the average. Particular care should be taken to assure that a disproportionate fraction of the average dose is not received by the most sensitive population elements. Specifically, it would be inappropriate to average the dose between children and adults, especially if it is believed that there are selective factors making the dose to children generally higher than that for adults.

5.5 When the size of the population group under consideration is sufficiently large, consideration must be given to the contribution to the genetically significant population dose. The Federal Radiation Council endorses in principle the recommendations of such groups as the NAS-NRC, the NCRP, and the ICRP concerning population genetic dose, and recommends the use of the Radiation Protection Guide of 5 rem in 30 years (exclusive of natural background and the purposeful exposure of patients by practitioners of the healing arts) for limiting the average genetically significant exposure of the total U. S. population. The use of 0.17 rem per capita per year, as described in paragraph 5.4 as a technique for assuring that the basic Guide for individual whole body dose is not exceeded, is likely in the immediate future to assure that the gonadal exposure Guide is not exceeded. The data in Section III indicates that allocation of this population dose among various sources is not needed now or in the immediate future.

A major difficulty has been the misinterpretation of these standards, particularly in the public mind. The intent as stated is that no individual in the general population should receive whole-body exposure of more than 0.5 rem/year and that the average exposure of population groups should not exceed 0.17 rem/year. What is often not realized is that one or the other of these limits may be governing depending on the nature of exposure. For example, if the exposure were to arise from specific locations such as nuclear power plants or reprocessing plants and it were assured that no individual at the boundaries of the installations could be exposed to more than 0.5 rem/year, it would be physically impossible for the U. S. population averages to approach anywhere near the level of 0.17 rem/year from such sources. Accordingly, we feel (disregarding numerical values) that both individual and average population guidelines should be maintained but that clarification should be included as an integral part of the regulatory statement.

In addition to individual and average population guidelines, we recommend that an additional limitation be formulated (not as a basic standard but for generating guidance) that takes into account the product of the radiation exposure and the number of persons exposed; this might be expressed in terms of person-rems. This need arises from acceptance of the non-threshold approach in risk estimates which implies that absolute harm in the population will be related to such a product. Operationally, for example, there would be advantage in assessment of trade-offs in connection with the siting of nuclear installations as related to the population densities of areas under consideration.

The above recommendations could be implemented with present knowledge. We now come to an important area that requires newer approaches. It is suggested that numerical radiation standards be considered for each major type of radiation exposure based upon the results of cost-benefit analysis. As a start, consideration should be given to exposures from medical practice because of present relatively high levels of exposure and from nuclear power development because of future problems of energy production and the need for public understanding.

With the development of modern health care programs in the Western world, there has been a marked increase in the use of radiation in the healing arts—medical diagnostic radiology, clinical nuclear medicine, and radiotherapy. This has resulted in the recognition that medical radiation now contributes the largest fraction, by one or two orders of magnitude, of the dose from man-made radiation to the United States public. In 1970, it is estimated that 129 million persons, or 63% of the population in the United States, received 210 million diagnostic radiological examinations, i.e., a rate of 68.5 examinations per 100 persons, and an increase of about 2% per year since 1964. The exposure rate is further increased by the estimated 8 million pregnant females at risk during the year 1970. At present, the estimated dose which is genetically significant to the population is of the order of 30 to 60 mrem per person per year, i.e. about 50% the level of natural radiation exposure in the United States. The significance of this lies in the absolute reduction of exposure that could be brought about at relatively low cost with no reduction in medical benefit and in addressing four important issues which center on the continued growth of health care delivery in this country. (a) At present, it does not appear feasible that the large number of variables involved in the use of radiation in health care to the public permit valid efficacious guidelines for medical practice. However, there is convincing evidence that certain nonselective mass screening radiographic procedures do not provide sufficient diagnostic health rewards for costs incurred, e.g., mass chest radiography for carcinoma of the bronchus and possibly for pulmonary tuberculosis, mass gastric radiography, routine pre-employment radiography for insurance purposes of some foodhandlers, and possibly screening mammography. (b) Attention must be directed toward the reduction of medical radiation dose to the pregnant or potentially pregnant female, in view of the evidence for significantly greater radiation sensitivity of the developing ovum and fetus. (c) Significant reduction of mean genetically significant dose can be brought about through programs of education, improvement of equipment, and certification of all persons in the healing arts who use radiation for diagnosis and therapy. Special attention should be given to testis shielding. On the basis of mouse data, we would expect the human male to be much more susceptible to radiation-induced mutation than the female. Also, the genetically significant dose of medical radiation is about twice as great in males as in females. For these two reasons, testis shielding, which is relatively simple, could reduce the number of radiation-induced mutations to a small fraction of the present number. (d) Control and regulation of present and future technological equipment responsible for medical exposure may be among the most feasible avenues to effect a continued reduction of dose due to medical radiation exposure.

The difficulties in attaining a useful cost-benefit analysis for nuclear power are formidable and will require interdisciplinary approaches well beyond those that have yet been attempted. Areas that require evaluation include: (a) projection of energy demands, (b) availability of fuel resources, (c) technological developments (clean combustion techniques, coal gasification, breeder reactors, fusion processes, magnetohydrodynamics, etc.), (d) public health and environmental costs of electrical energy production from both nuclear and fossil fuel including aspects of fuel extraction, conversion to electrical energy, and transmission and distribution.

Chapter III

SOURCES OF IONIZING RADIATION AND POPULATION EXPOSURES

I. Introduction 12
II. Natural Background Radiations 12
III. Medical Exposures 13
  A. Medical and Dental Radiology 13
  B. Diagnostic Use of Radiopharmaceuticals 14
  C. Summary of Medical Exposures 14
IV. Nuclear Power 15
  A. Projected Growth 15
  B. Estimated Exposures 15
    1. Uranium Mines 15
    2. Uranium Mills and Fabrication Plants 15
    3. Power Generating Plants 15
      (a) Normal Operations 15
      (b) Accident Conditions 16
    4. Fuel reprocessing plants 16
  C. Tritium 17
  D. Krypton-85 17
V. Nuclear Explosions 17
  A. Local Fallout from Atmospheric Tests 17
  B. Local Exposure from Underground Tests 17
  C. Worldwide Global Fallout 17
VI. Nuclear Ships 18
VII. Nuclear Rocket Development 18
VIII. Miscellaneous and Occupational Exposures 18
IX. Summary 18
References 19

Chapter III

SOURCES OF IONIZING RADIATION AND POPULATION EXPOSURES

I. Introduction

The scale and nature of past and foreseeable exposures are reviewed in order to provide a focus for risk estimates and because radiation protection guidance should ultimately take into account all sources of exposure. This discussion is not intended to be a critical, comprehensive, or independent review, and is included only for information and convenience of reference. The Special Studies Group, Office of Radiation Programs, Environmental Protection Agency is preparing a detailed review and their draft material (*1*), kindly made available to us, has served as a major basis for the present statement. Except as otherwise referenced, material in this chapter is drawn from the report of the Special Studies Group. Estimates of present and past exposures are thought to be accurate within a factor of two; projections have uncertainties probably within an order of magnitude. It is considered useful, nevertheless, to have available some estimate of possible exposures, indications of which processes are liable to produce various types of exposures, and particularly information as to changes that could be made to reduce exposures effectively.

II. Natural Background Radiation

External exposure from natural background comes primarily from cosmic radiation and terrestrial gamma radiation. Dose equivalent rates from these sources vary because of altitude, latitude, and differences in amounts of natural radioactive material present in the earth. For example, cosmic radiation increases by a factor of three in going from sea level to 10,000 feet, and by 10 to 20% in going from 0° to 50° geomagnetic latitude.

Internal exposures arise from body deposition of radionuclides that have been inhaled or ingested. The major contributor from inhalation is radon and its daughter products, and from ingestion, potassium-40.

Table 1 presents estimated total annual average whole-body doses from natural radiation in the United States (*2*). The dose equivalent rate for cosmic radiation ranges from 38 mrem/yr in Florida to 75 mrem/yr in Wyoming. Terrestrial gamma dose rates range from 15 to 35 mrem/yr for the Atlantic and Gulf Coastal Plains to 75 to 140 mrem/yr for the Colorado Plateau. Taking into account shielding by building structures and overlying tissue, it has been calculated that the average gonadal dose is about 90 mrem/yr (*2*).

Table 1

Estimated Total Annual Average Doses from Natural Radiation in the United States (Whole-body)

Source	Annual Doses
Cosmic Rays	44
Terrestrial Radiation	
External	40
Internal	18
Total	102

III. Medical Exposures

The use of radiation in the healing arts is recognized today as the largest man-made component of radiation dose to the United States population. Contributions from this source include medical diagnostic radiology, clinical nuclear medicine, radiation therapy, and occupational exposure of medical and paramedical personnel.

A. Medical and Dental Radiology

Estimates of the annual genetically significant dose (GSD) to the U.S. population from medical and dental radiology range from 18 to 136 mrems. This variation is influenced by relative child expectancy, age and sex distribution of the subjects, usage distribution of specific examinations, and gonad dose per examination. On the basis of the study of a large segment of the population in 1964, the Public Health Service estimated an annual GSD of 55 mrems (*3*); it was further estimated that 80% of this dose was due to x-ray examinations of males above age 15 and that 95% was due to abdominal examinations of both males and females. About 96% of the dose was contributed by radiography, 4% by fluoroscopy, and less than 1% by photofluorography.

Estimates have been made of future doses. Data indicate that film sales between 1945 and 1965 increased at a rate of 5.4% per annum. A study in selected hospitals indicates that between 1963 and 1968 the annual rate of discharges of patients in any diagnostic radiation category and in total diagnostic radiation categories increased by 3.6% and 6.6%, respectively. Public Health Service studies show that the examination rate for medical diagnostic radiography increased from 61.8 examinations per 100 persons in 1964 to 68.5 examinations per 100 persons in 1970, about 2% increase per annum. In summary, it can be estimated that the per annum increase in the rate of delivery of radiographic procedures ranges between 1% and 4%.

Other factors which are relevant to the projected population dose from medical radiography include potential reductions which may be accomplished through improved collimation and radiographic techniques. Studies have shown that dose reductions of as much as 30% could be accomplished through improved techniques. This is inclusive of 10% of unnecessary radiation due to repetitive examinations. Gonadal shielding is particularly important in the reduction of male gonad doses and data show that use of proper shields can reduce this dose by as much as 90%. Proper collimation can result in reductions of the genetically significant dose by about 65%. However, in practice, this is not accomplished easily, or carried out routinely, since it requires care in positioning the patient and x-ray tube as well as selection of proper cone for x-ray field size adjustment. Considering all of these factors, experts estimate that it appears reasonable that as much as a 50% reduction in the genetically significant dose from medical radiology might be possible through improved technical and educational methods. On the assumption that technical improvements keep pace with the increased usage of radiation in medical radiology, it appears reasonable to estimate that the mean per capita radiation dose within the next several decades will remain fairly stable.

Estimates of specific organ doses are generally not yet available for the United States. As a first step in estimating approximate relative somatic dose one might determine the mean dose in the center of the abdomen. This index, the "Abdomen dose" has been calculated from dose estimates, ovarian (for females) and "simulated ovarian" (for males), weighted for their representation in the U.S. population. Because the entire population, regardless of age, is used, the data are not weighted for future child bearing potential, and the dose estimates are not sensitive to small variations in beam size and position, the difficulties encountered in determination of the GSD are reduced. Furthermore, one is able to calculate dose estimates for the exposed population (i.e. considering only persons receiving x-ray examinations). The biological significance of the "abdominal dose" has not been evaluated. The unequal distribution of body area exposed, the non-homogeneity of human tissue, and variations of dose with age all preclude such application. In 1970, based on preliminary information, the abdominal dose due to medical radiography appears to have risen. This increase, due entirely to an elevation of the female per capita abdominal dose, requires elucidation. For the whole U.S. population, the annual per capita abdominal doses for 1964 and 1970 are estimated to have been 61 and 72 mrem, respectively. Errors in the survey and the measurements from which these estimates were derived have not, as yet, been fully evaluated. Accordingly, it appears that the most prudent conclusion is that this index has remained relatively stable during this interval.

Dental x-ray visit rates during 1961 and 1964 were similar, with a slight decrease during the latter year being attributable to sampling differences. Between 1964 and 1970, a gradual rise of about 4% per annum in the annual rate of dental x-ray visits was evident. Using a per capita dental x-ray visit rate of 0.27 and an average of five films per visit, the predicted somatic person-rem to the United States population from dental x rays in the year 2000 will be less than 0.2×10^6.

B. Diagnostic Use of Radiopharmaceuticals

An early estimate (1956) of genetically significant dose from medical uses of radionuclides indicated a dose of 8 mrem per person per year, based on the total quantity of ^{131}I and ^{32}P shipped during the year. A subsequent analysis (1957) assuming a diagnostic examination rate of 150,000 to 200,000 per year using ^{131}I, of which probably not more than 25,000 examinations were performed per year on patients below age 30, indicated the genetically significant dose would be equivalent to 0.004 mrem. An equal genetically significant dose was alleged to the accrued through other diagnostic radionuclide procedures for a total annual GSD of 0.008 mrem (*1*).

More recent information yielded an estimated total accumulated gonad dose of 195,000 rem (sum of doses to all exposed individuals) from all diagnostic radiopharmaceutical procedures to all age groups. Again, if one assumes that 12.5% of the individuals receiving these procedures are below age 30, and that 50% of the total population is also below age 30, then the estimated annual GSD is 0.26 mrem from the diagnostic use of radiopharmaceuticals.

Studies of radiopharmaceuticals indicate increases in the rate of administrations of between 15 and 20% per year in the mid-1960's. More recent information based on sales of radiopharmaceuticals indicated an annual increase of 25% per year. It appears judicious to estimate that in the 1960's the use of radiopharmaceuticals increased fivefold during the 10-year period and that an increase of sevenfold may be experienced in the next 10 years. Thereafter, it is difficult to make predictions, especially in terms of dose since technical changes are likely to play a large role in dose reduction in so rapidly changing a field. Assuming no technical changes, and the growth pattern indicated above, it is expected that the whole-body dose to the United States population in 1980 from diagnostic use of radiopharmaceuticals will be 3.3 million person-rem. Even with a slowing of the rate of increased use of radiopharmaceuticals the accrued whole-body man-rem could easily reach 15% of the total somatic dose from all man-made souces by the year 2000.

Improvements in equipment have led to decreased dosage requirements in thyroid function tests and kidney scans, and the substitution of radionuclides yielding lower patient exposure have already reduced total body and kidney doses per procedure. Even with these improvements, in the 4-year period 1964 to 1968, one institution reports that the average whole-body dose per patient increased from 100 mrem to 160 mrem due to the increased use of radiopharmaceuticals.

C. Summary of Medical Exposures

Published literature shows that the Genetically Significant Dose to the U.S. population from medical and dental radiation in 1964 was 55 mrem (*3*). A preliminary estimate of the value for 1970 is 36 mrem (*4*); however, the uncertainty surrounding the GSD results for 1964 and 1970 have not as yet been calculated. Estimates indicate that the annual per capita "abdominal dose" from these sources to the whole population was 72 mrem in 1970. It appears that the mean "abdominal dose" for the U.S. population as determined in 1964 and 1970 has remained relatively stable during the interval. As with the GSD, because the uncertainty has not been calculated, the magnitude of whatever change may have occurred has not been determined. The main contributor of the total dose from medical exposures is diagnostic x-radiation, the contribution from dental radiation and radiopharmaceuticals being far lower. Radiation therapy in the treatment of cancer was estimated to contribute an additional 5 mrem to the GSD annually. Based on information presently available, it appears that the mean per capita radiation dose from diagnostic medical radiology could remain stable in future years, if technical improvements keep pace with increased usage rates.

IV. Nuclear Power

A. Projected Growth

There are great pressures for growth of the nuclear power industry. These include: demand for electricity, potential shortages of certain types of fossil fuels, and the effects of present modes of producing electricity on health and the environment. The extent to which the nuclear industry will grow depends upon technology development, establishment of its health and environmental costs, and public acceptance. As a point of departure the Special Studies Group of the Environmental Protection Agency (*1*) has assumed that nuclear capacity in the United States will increase from 6000 megawatts in 1970 to 800,000 megawatts in 2000. Associated with this increase there is a postulated 25-fold increase in uranium mining and milling, a 15-fold increase in fuel fabrication facilities, and establishment of about 15 commercial fuel reprocessing plants compared to one now in existence. For purposes of dose projections, the Special Studies Group has also assumed that a limit of 5 mrem per year per reactor at the site boundary will be met.

B. Estimated Exposures

1. Uranium mines

The mining of uranium, while increasing the amount of uranium and its radioactive decay products accessible to man, has not been found to cause measurable increases in environmental radioactivity outside the immediate vicinity of the mines. The primary problem in underground uranium mines is known to be the inert gas radon 222 and its short-lived daughters; physical attachment of the daughters to airborne dust particles is probably the most significant process. It is possible that long-term effects of later daughters, especially bismuth-210, lead-210, and polonium-210, could be of importance as the latter two appear to move readily through the biosphere. Whereas these operations are not considered as contributors to general environmental contamination there have been serious health problems among underground uranium miners and these matters are discussed in detail in a later chapter.

2. Uranium mills and fabrication plants

The extraction of uranium from ore produces by-products or tailings and waste that can constitute a source of environmental radiocontamination, primarily ^{226}Ra and its decay products. ^{226}Ra is rather insoluble in water but does dissolve slowly and enters the biosphere especially in water and aquatic biota. Deposition in crops from irrigation water has been observed. The location of uranium mills in sparsely populated areas and appropriate control of tailings and liquid waste on restricted areas can prevent population exposures from this source. Tailings have been used in the past for public construction in certain communities. Presumably this will not happen again.

Fuel fabrication can be and is carried out in such a way as not to increase levels of radioactivity in the environment.

3. Power generating plants

(a) Normal Operations

The principal radionuclides in present reactor effluents are ^{3}H, ^{58}Co, ^{60}Co, ^{85}Kr, ^{89}Sr, ^{90}Sr, ^{131}I, ^{131}Xe, ^{133}Xe, ^{134}Cs, ^{137}Cs, and ^{140}Ba. The amounts released depend greatly upon the type and design of the reactor. Gaseous and volatile nuclides such as ^{85}Kr, ^{131}Xe, and ^{133}Xe contribute to external gamma dose as a result of immersion; the others contribute to the dose externally by surface deposition and internally via the food chain. The most important stack discharges from reactors are radionuclides of noble gases in the elemental form, tritium as water vapor, and iodine in a variety of forms such as elemental or organic compounds. The noble gases are metabolically inert in contrast to the tritium and iodine compounds. Liquid wastes from reactors contain tritium as HTO and activation radionuclides of iron, cobalt, nickel, and zinc. The latter may be oxidized or complexed to affect solubility.

If and when Liquid Metal Fast Breeder Reactors (LMFBR) become commonplace, other radionuclides will become sources of environmental contamination including ^{239}Pu, ^{238}Pu, ^{241}Pu, ^{24}Na, and ^{22}Na. Normal release rates are expected to be low but the implications of handling large amounts of radioactivity and of accidents will have to be taken into account.

External dose rates from power reactor effluents have been estimated by computer models assuming whole-body gamma doses of 5 mrem/year at each reactor boundary. The annual average dose to the U.S. population was estimated to be 0.002 mrem for the year 1970 and 0.17 mrem for the year 2000. Predictions could be high because of improvement in technology or could be low if plant performance deteriorates with time; also no account is taken in this calculation of the possibility of local exposures due to accidents.

Consideration of internal exposures leads to two conclusions: (a) the principal radionuclide will be ^{131}I; (b) internal doses will be much lower than the overall external gamma radiation doses.

(b) Accident Conditions

Nuclides escaping from reactors under design basis accident conditions may be classified as volatile or non-volatile. The former include noble gases, iodine and tritium, whose behavior is as previously described. Nonvolatile nuclides of importance include all fission products, many activation products, uranium, and plutonium. Inhalation with dependency on particle size will probably be more important than exposure via environmental contamination. In an LMFBR the initial inhalation problem will arise from plutonium with long-lived ^{22}Na becoming subsequently of more concern.

For a light water thermal power reactor, the major catastrophic event which could result in the release of large quantities of radioactive materials to the environment would be the loss of coolant accident. Although the absence of water moderator would stop the fission process, the decay heat due to the inventory of radioactive material could result in a meltdown of the reactor core.

Most power reactors have provisions for an emergency core cooling system, but questions have been raised (*5-8*) as to the ability of such systems to prevent a meltdown. If there were a loss of coolant accident or if the cooling system were damaged by sabotage, the effectiveness of the emergency cooling system would be critical. Unless this system provides adequate cooling water in a very short time, the fuel in the reactor core would certainly melt and the molten material would break through the containment vessel. If this were to happen, substantial quantities of gaseous and volatile and nonvolatile fission products would escape to the atmosphere in the form of a radioactive cloud, and could cause considerable radiation exposure to people downwind from the reactor site. The total number of individuals who could receive serious damage in a single accident of this type, if it should occur, is likely to be considerably larger than from all of the predicted design-basis accidents.

This Committee is not competent to estimate the frequency of such accidents, to assess the severity of effects that could occur, or to recommend the extent of preventive measures that should be taken. It seems clear, however, that considerable effort and expenditures are warranted to reduce these risks and will, in fact, be required if the nuclear power industry is to develop in conformance with protection of the public that is required, taking into account the design and engineering needs commensurate with the potential for damage.

4. *Fuel reprocessing plants*

From fuel reprocessing plants, the most important gaseous effluents include tritium as HTO, noble gases especially ^{85}Kr, elemental iodine, organic iodides, and probably such forms as NOI and HIO. Short-cooled fuels may contain ^{131}I, all fuels will contain ^{129}I. Liquid effluents from reprocessing contain radionuclides of cesium and strontium, tritium as HTO, other long-lived fission products including the rare earths and possibly plutonium. Cesium and strontium are relatively soluble and metabolically available. The rare earths, zirconium, and niobium tend to be insoluble and metabolically inert.

Dose calculations for population exposures from nuclear fuel reprocessing are greatly dependent on the assumptions made. It has been estimated by the Special Studies Group that the average annual whole-body dose to the

U.S. population from fuel reprocessing was 0.0008 mrem in 1970 and will be 0.2 mrem in the year 2000; the tissues of major exposure are the respiratory lymph nodes, the thyroid gland, and skin. Skin and whole-body doses from ^{133}Xe and thyroid doses from ^{131}I could be reduced by longer decay times before reprocessing; ^{129}I would still need to be removed as well as ^{85}Kr if possible. Improved particulate removal could reduce the dose to the respiratory lymph nodes.

C. Tritium

Tritrium and krypton-85 should be assessed on a basis of worldwide production because of their distribution patterns. Tritium is distributed throughout the surface waters of the world and is of concern to man through any exposure involving water. The sources and relative contributions to the world inventory in 1970 expressed as megacuries of tritium are roughly as follows: reactor produced, 0.5 to 1; naturally produced, 10 to 10^2; nuclear explosions, about 10^3. Tritium from the nuclear power industry is not expected to reach levels equal to those resulting from past weapons-tests until about the year 1990. The annual dose from worldwide tritium is estimated to be 0.04 mrem/person in 1970 and 0.03 mrem/person in the year 2000. In 1970, the concentrations of tritium in the oceans and surface and ground waters in the U.S. typically ranged from 0.2 - 1.5 nanocuries/liter.

D. Krypton-85

Krypton-85, a noble gas, is distributed throughout the atmosphere and is a source of exposure to man both externally and through inhalation. Production of krypton-85 naturally by cosmic rays and artifically by weapons detonations is very low compared to production by the nuclear power industry. The world inventory from nuclear explosives is calculated to be about 3 MCi; reactors are already producing more than 10 megacuries/yr.

The concentration of ^{85}Kr in air has been estimated as 15 pCi/m^3 for 1970. The estimated annual whole-body doses to the U.S. population from worldwide distribution of ^{85}Kr are 0.0004 mrem/person in 1970 and 0.04 mrem/person in the year 2000. Skin doses are calculated to be about 50 times greater and lung doses twice as great as whole body doses.

V. Nuclear Explosions

A. Local Fallout from Atmospheric Tests

As an example of local fallout, calculations have been made for exposures in the vicinity of the Nevada Test Site for the period September 15, 1961 to September 15, 1962. This was the period of resumption of atmospheric nuclear tests following the moratorium of 1958. The exposures are estimated as 47 mrem external gamma dose to a population of 18,000; 10 mrem whole body dose from ^{137}Cs to a population of 792,000; 9 mrem to the thyroids of the same population. These sum to a total of 8766 person-rem to the whole body.

B. Local Exposure from Underground Tests

As examples of exposures from underground tests and applications of nuclear devices, mention is made of two specific events. During the "Gnome" test (December 10, 1961) some venting occurred to produce mainly a gaseous effluent. Radioactivity was detected only within about 10 miles of the test site. External gamma dose from the cloud gave a total of 30 person-rem to a population of about 45,000; there were no internal radiation exposures as judged by analysis of environmental samples.

During the gas production phase of the "Gasbuggy" test, radioactivity in which only tritium, ^{14}C and ^{85}Kr were detected, was released from the well. No radioactivity was detected beyond 10 miles from the well and there are no populated sites within that area.

Experimental programs have progressed to some extent along lines of excavation, gas stimulation, recovery of oil from shale, mineral recovery, underground storage, waste and water management, and use of geothermal energy. There is no basis for protection of population exposures from such activities and estimates would need to be made on an individual basis.

C. Worldwide Global Fallout

Worldwide fallout is mainly a result of large-scale high-yield atmospheric tests conducted by the U.S. and U.S.S.R. prior to 1963; during the past several years the relatively small tests conducted by the French and Chinese have maintained an annual fallout deposition that has been relatively constant.

The total annual whole-body doses from global fallout in mrem/person ranged from 13 in 1963 to 4.0 in 1969. As an example, the contributions to the total dose of 4.0 mrem/person in 1969 were: 0.9 mrem external gamma; 2.1 mrem from ^{90}Sr; 0.4 mrem from ^{137}Cs; 0.6 mrem from ^{14}C. It should be emphasized that these are average values and actual values could vary by more than factors of 2 because of variation in fallout and diet. If the rate and type of testing from 1965-1970 continues, the annual dose is calculated to reach 4.9 mrem/person in the year 2000.

VI. Nuclear Ships

In 1970, the United States had in operation 96 nuclear powered vessels, 92 submarines and 4 surface ships. About 0.024 Ci of radioactivity were released in liquid wastes in 1970 including ^{187}W, ^{51}Cr, ^{181}Hf, ^{59}Fe, ^{55}Fe, ^{95}Zr, ^{182}T1, ^{54}Mn, ^{58}Co, ^{60}Co.

VII. Nuclear Rocket Development

From 1959 through 1969, 31 nuclear reactor rocket engine tests were conducted at the Nuclear Rocket Development Station. External gamma doses were too low to be significant. Thyroid doses from ^{131}I and ^{133}I were calculated to be about 3 mrem to a population of about 740,000 or about 2100 person-rem during the 10-year period.

VIII. Miscellaneous and Occupational Radiation

The contribution of miscellaneous radiation sources such as television, consumer products, and air transport, to average whole-body doses are as follows: 2.0 and 2.6 mrem/yr for 1960 and 1970, respectively. Projected doses are 2.1 mrem for 1980 and 1.1 mrem for 1990 and 2000. The extent of occupational exposures to radiation is grossly estimated as follows: total per capita dose - 0.8 mrem/yr; mean dose per worker - 200 mrem/yr; number of workers - about 3/4 million; total person-rem/yr - 0.16 million. Most of this dose was incurred through the use of ionizing radiation in the practice of medicine and dentistry. If the projections made by the Special Studies Group (*1*) are accepted, increases in nuclear power production over the next several decades are expected to increase the average per capita dose by only about 0.1 mrem/yr.

IX. Summary

Table 2 presents a summary of estimates of whole-body radiation doses[1] It is clear that major contributors to radiation dose are natural background and medical applications. By far the greatest portion of man-made radiation dose to the U. S. population is due to exposure accrued during medical diagnostic procedures. Medical diagnostic radiology accounts for at least 90% of the total *man-made* radiation dose to which the U.S. population is exposed. This is at least 35% of the *total* radiation dose from all sources (including natural radioactivity). On the average, according to the EPA report (*1*) the contribution from the developing nuclear power industry is expected to contribute a population dose of less than 1% of natural background. Therefore, in order to ascertain the radiation effects on the population of nuclear power development, risk estimates must be made for levels of a few millirem per year.

It must be emphasized that the estimated radiation doses as presented in summary form, although the best now available, must be regarded for what they are - rought estimates subject to uncertainties of projection and engineering performance.

To assess the effects of the radiation exposure it is important also to take into consideration the higher doses that might be received by sub-sets of the population; such matters have to be dealt with on an individual case basis. In addition, there are some areas of uncertainty in regard to nuclear power which cannot be

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[1] Except for medical diagnostic radiation, which is based on the abdominal dose.

Table 2

Summary of Estimates of Annual Whole-Body Dose Rates in the United States (1970)

Source	Average Dose Rate* (mrem/yr)	Annual Person-Rems (in millions)
Environmental		
Natural	102	20.91
Global Fallout	4	0.82
Nuclear Power	0.003	0.0007
Subtotal	106	21.73
Medical		
Diagnostic	72**	14.8
Radiopharmaceuticals	1	0.2
Subtotal	73	15.0
Occupational	0.8	0.16
Miscellaneous	2	0.5
TOTAL	182	37.4

*Note: The numbers shown are average values only. For given segments of the population, dose rates considerably greater than these may be experienced.

**Based on the abdominal dose.

assessed by this Committee. These include: (a) engineering matters such as possibilities of failure of plants to meet anticipated levels of performance or deterioration of plant performance with time, (b) large scale management of radioactive wastes, (c) probabilities and effects of catastrophic accidents, (d) possibilities of sabotage and diversion of fissionable material.

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Chapter IV

ENVIRONMENTAL TRANSPORT AND EFFECTS OF RADIONUCLIDES

I. Introduction 22
II. Radionuclides in Air 22
  A. Air Quality Assessment 22
  B. Atmospheric Dispersion and Removal Processes 23
  C. Natural Radionuclides 24
  D. Land-based Nuclear Facilities 24
  E. Marine-based Nuclear Facilities 24
  F. Atmospheric Testing of Nuclear Devices 24
  G. Underground Venting 24
  H. SNAP Devices 25
III. Aquatic Systems 25
  A. Natural Radioactivity 25
  B. Acute Radiation Exposure 25
  C. Chronic Radiation Exposure 25
  D. Internal Emitters 26
  E. Environmental Factors and Radiation Effects 26
  F. Radiation Effects on Populations 26
IV. Soil-Plant Systems 27
  A. Natural Radionuclides 27
  B. Radioactive Fallout 27
  C. Other Sources of Radiocontamination 28
  D. Redistribution of Radionuclides 28
  E. Radiation Effects in Soils 29
  F. Radionuclide Entry into Plants and Radiation Effects 29
V. Animals and Animal Products 31
  A. Relative Radiosensitivities 31
  B. Routes of Exposure of Animal Populations 31
  C. Animal Products as Sources of Human Exposure 32
    1. Milk and Milk Products 32
    2. Meat 33
    3. Poultry 34
VI. Summary — An Ecological Approach 34
References 35

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Chapter IV

ENVIRONMENTAL TRANSPORT AND EFFECTS OF RADIONUCLIDES

I. Introduction

Previous considerations of radiation protection have by and large ignored any possible effects of radiation on the environment - on organisms other than man. It has been assumed that at levels of radiation acceptable to man from past events there would be no observable biological effects on other individual organisms, and, furthermore, that there would be no effects on populations even if there were undetectable effects on individual organisms. Thus, the practice has been to limit monitoring and observation to those parts of the ecosystem close to man. It is well known, however, that various chemical pollutants have caused definite effects on plant and animal life at ambient levels that have been traditionally and legally accepted by man. Therefore, our emphasis has been on the possible direct environmental effects from radiation. Pertinent data on this subject have been reviewed in detail.

With the development of nuclear energy, it is inevitable that the biosphere will be exposed to an increasing burden of radiation. For living species other than man, we need an estimate of the amounts and kinds of radiation that can be tolerated by the individual organism, the population, and the ecosystem without significantly changing the "balance of nature." The situation is most complex because: (a) balance responds to a multiplicity of natural and man-made factors of which radiation is but one; (b) knowledge is extremely limited on the response of ecosystems to small changes in the governing factors; (c) interactions may be of great importance and practically nothing is known about them; (d) with a few notable exceptions, there are few data on radiation effects on various species, especially on genetic effects.

The same general types of radiation effects as described extensively for man in later chapters are expected in all living systems. However, radiation protection guidance for man rests on ethical consideration of the individual. For other living species the concern is not for the individual but for the population. Primarily for reasons of natural selection, it seems likely that genetic effects of radiation would be relatively unimportant and that effects on general mortality and fertility would be controlling.

In addition to the problem of direct radiation effects on the environment, it is important to understand the transit of radioactivity in ecosystems wherever it occurs. This information is needed for several reasons: (a) to enable calculation of concentrations of radioactivity that will reach man via biospheric pathways: (b) to permit mitigation of direct effects on human populations, especially following accidental events; (c) to indicate any particular species that might be exposed to unusually high levels; (d) to enable predictions of population exposures that might occur from given levels and patterns of contamination; (e) to serve as a basis for practical and effective monitoring systems. Information on transport relatable to testing of nuclear devices is dealt with only briefly because these matters have been covered at great length in the scientific literature; more attention is given to situations that could arise from nuclear activities other than testing.

II. Radionuclides in Air

A. Air Quality Assessment

Air is the transport medium which carries radionuclides released to the atmosphere from the sources as described in Chapter III to the receptors of interest in the biosphere. A comprehensive document in this area is "Meteorology and Atomic Energy" edited by D. H. Slade (*1*). The relationship of air quality to environmental impact requires an assessment of the amount and nature of radionuclides released, of air concentrations integrated over the time of interest, and of deposition or contamination patterns determined from atmospheric and geographical conditions (*1-6*). Mathematical simulation of concentration distributions has been more helpful generally than actual measurements of air quality because the requirements of time and space sampling for the latter are difficult to fulfill adequately. Efforts at modeling have been reviewed in detail (*7-10*). In the future, more attention may need to be given to development and implementation of sampling procedures.

Air quality measurements are normally required to survey distribution of pollutants in anticipation of control strategies, to collect data for research purposes - environmental models, etc., or to document air quality conditions for public record (*11*). It is useful to have measurements of both air quality and meteorological parameters. These measurements can be used for radiation-dosage calculations (*12*). The mode of calculation depends upon whether the major effect is from the total radiation received from the cloud, instantaneous peak concentrations or a combination of radiation dose from the passing of the cloud and from contaminated surfaces following the passage.

B. Atmospheric Dispersion and Removal Processes

To understand the dispersion of radionuclides in the atmosphere, two processes must be considered, transport and diffusion. From so-called "instantaneous" releases, such as explosions or short ventings the puff of material moves away from the source with a speed and direction determined by the wind at the moment of release (*1, 5, 13-15*). Surface air concentrations decrease with sampling time downwind of a source due largely to horizontal dispersion. For evaluating the impact of continuously emitting sources, relationships for periods of days are important. Reliable estimates of average concentrations or exposures can be made from routine meteorological observations and appropriate diffusion equations (*1, 5, 16-20*). Understanding of factors governing global dispersion are limited although calculation techniques have been described (*1, 21, 22*).

Atmospheric concentrations of radionuclides can be corrected for radioactive decay by multiplication factors that consist of the simple exponential term in the case of a single nuclide of known half-life or by appropriate power factors for mixtures of radionuclides.

Surface dry deposition can occur by gravitational settling (fallout), surface impaction, electrostatic attraction, adsorption, and chemical interaction. Two empirical approaches have been used to study this process. Deposition velocities have been defined as the ratio of deposition rate to immediate ground level air concentration (*23, 24*). The other technique is to derive the deposition velocity from a material balance involving the mass flux of material through a vertical plane perpendicular to the mean wind direction. It appears that for particles less than 10-15 micron diameter, the relative effects of impaction, diffusion and adsorption are more important; conversely, larger particles fall to the ground within rather short travel distances (*25, 26*).

Removal of airborne radionuclides can occur by precipitation scavenging (*1, 27*), that is by rainout or snowout (in-cloud scavenging), or by washout (scavenging below the cloud by rain or snow). Radionuclides released from the ground will be transported by low level winds and diffused upward by turbulent eddies with removal primarily by washout at close-in distances and by rainout at longer distances. Releases from high elevations (stratosphere) will be dispersed by the general circulation and tropospheric exchange processes will control subsequent removal. Washout by rain is generally insignificant for particles smaller than about 1 micron diameter. Washout of reactive gases can be predicted by using the theory of molecular diffusion to water drops. Snow is apparently as effective as, to several times more effective than, rain at the same precipitation rate. Formal mathematical techniques for predicting precipitation scavenging are available but must be used with caution.

C. Natural Radionuclides

Most of the natural radioactivity in the atmosphere is due to radon and its daughter products, ^{218}Po, ^{214}Pb, ^{214}Bi, and ^{214}Po which become attached to submicron aerosols. Radon and its decay products have been most useful for studies of dispersion within the first 100 meters above ground and have shown promise as tracers of tropospheric transport on a hemispheric scale (*28*).

Radon concentrations at ground level usually range from 10 to 1000 picocuries per cubic meter for continental areas; the higher concentrations (500-1000 pCi/M^3) usually occur for periods of less than 24 hours as a result of stagnant weather conditions (*29, 30, 31*). Higher concentrations may also occur over areas exposed to uranium ore tailings or natural uranium outcroppings. Air concentrations over oceans may be lower than those over ground by two orders of magnitude.

D. Land-based Nuclear Facilities

Past studies of stack effluents from nuclear power and reprocessing plants have shown that almost all atmospheric releases are either gaseous or consist of particles less than 1 micron diameter. These emissions are of the so-called elevated point source type and are treated by the conventional Gaussian diffusion formulation. The stack emission is likely to increase rapidly during the dissolving of fuel and subsequently subside. Even low-level stack emissions will require consideration of average and atypical weather patterns for describing concentration distribution.

E. Marine-based Nuclear Facilities

There is a trend toward siting reactors along seacosts or large bodies of water. Quantitative information pertaining to movement of airborne material over ocean and shoreline complexes, especially in regard to reactor siting, has been reviewed (*13, 32, 33*). Intuitively, one would expect atmospheric diffusion rates over extensive water surfaces to be less than for diffusion overland. Any assessment of atmospheric dispersion in coastal areas must consider the land-sea breeze phenomenon; information for individual sites is not usually available. Important factors include time of day, season, comparative water and air temperatures, and local topography. The diffusion climate of each site must be studied individually.

Nuclear power ships and submarines may represent a moving source with respect to potential radionuclide releases to the air. This makes any calculation of predictions very difficult.

F. Atmospheric Testing of Nuclear Devices

The planning of nuclear tests and their safe execution require prediction and measurement of meteorological phenomena (*22, 34, 35*). The planning phase requires assessment of climatological data relevant to scheduling and monitoring as well as forecasts of dispersion and deposition patterns for released radionuclides. The second phase requires meteorological and air quality measurements as well as dispersion-fallout forecasts made during and immediately after the test.

For local fallout (within 100 miles) the most important information is accurate prediction of local wind, which can be gained from an observation network including the use of weather radar. For distances beyond 100 miles, Fickian diffusion theory can be used.

G. Underground Venting

When nuclear devices are detonated underground in cratering applications, most of the radionuclides are attached to particulate material and rapidly settle to the ground; however, some of the material is either gaseous or of sufficiently small size to remain airborne. In contained applications, any venting usually is in the form of a small continuous leak of volatile radionuclides.

The first step in assessment of venting is the determination of trajectories and various techniques are available including the central tendency method and kinematic methods (*35*). For cratering applications where the release is usually in the form of an instantaneous volume a specific dispersion model has been developed and usefully applied to a number of cratering tests.

H. SNAP (Systems for Nuclear Auxiliary Power) Devices

These systems represent potential problems of high-altitude sources of radionuclides. Experience from assessment of stratospheric dispersion from weapons test fallout is most useful. The techniques and shortcomings of forecasting dispersion in both the troposphere and stratosphere on a hemispheric or global scale have been well reviewed (*21, 22, 36, 37*).

III. Aquatic Systems

A detailed and comprehensive report entitled "Radioactivity in the Marine Environment" (RIME) (*38*) has recently been published by the Panel on Radioactivity in the Marine Environment of the National Academy of Sciences. It deals with sources of radionuclides, distribution, physical processes of water movement, chemical reactivity in seawater, sedimentary reactivity, radioecological interactions, distribution and effects of radionuclides in marine organisms, and implications for human radiation exposure. The present statement draws heavily upon the RIME report and emphasizes those considerations which need to be taken into account in protection of man and his environment through control of radiation.

A. Natural Radioactivity

Estimates for dose rates from total alpha activity to phytoplankton from the open sea ranged from 230 to 2800 mR/yr (*39*). Tissue doses in cod *Gadus callarias* and in haddock *Gadus aeglefinus* ranged from 8 to 27 mR/yr (*40*). The total dose rate to plaice, *Pleuronectes platessa* in the Irish Sea was estimated as 82 mR/yr with the seabed being the major source of radiation for this bottom-living species (*38*).

B. Acute Radiation Exposure

Lethal response to acute radiation varies among organisms because of physiological differences; in the aquatic environment there are additional variables such as temperature, dissolved oxygen, chemical composition, and salinity. Some generalizations can be stated: (a) exclusive of the eggs and larvae of invertebrates and fish, most of the aquatic organisms studied are relatively radioresistant; (b) marine and freshwater species are similar in radiation resistance; (c) primitive forms are more resistant than complex vertebrates and older organisms more resistant than young. Bacteria and algae may tolerate thousands of roentgens. The LD_{50} for adult rainbow trout, *Salmo gairdneri* ranged from 300 to 3000 R, and for the most sensitive stage of the developing trout egg the LD_{50} was as low as 16 R (*41*). There are few data for marine species; estimates for six species of adult fish ranged from 1050 to 5550 R (*42*). It has been pointed out that radiation response is more meaningfully expressed in terms of a time curve rather than a simple LD_{50} because various organisms have shown markedly different sensitivities as a function of time after radiation exposure (*43, 44*).

C. Chronic Radiation Exposure

A series of long-term experiments with chinook salmon, *Oncorhynchus tshawystcha*, indicated that irradiation at 500 mR/day from the fertilization to feeding stage (total dose 33-40R) did not reduce the reproductive capability over a period of slightly more than one generation (*45, 46*). Abnormalities in young fish were increased, but the number of adults returning was not affected. Total doses of 0.6 to 500 R to the eggs of plaice, *P. platessa* from fertilization until hatching produced no significant effects in survival at hatching or in production of abnormal larvae (*47, 48*). Young blue crabs were exposed to 5105, 11502, or 45693 rads over a period of 70 days; deaths due to radiation occurred at the highest dose but not at the others (*49*).

Experimental data on the radiation effects on eggs in contaminated media are conflicting, mainly, it is thought, because of difficulties in successful maintenance under controlled environmental conditions. Most of the work has been done using ^{90}Sr and making observations of morphological abnormalities, delay in development, and mortality. Practically all workers have seen effects in the range of 10^{-4} Ci/liter whereas some have and some have not seen effects in the range of 10^{-4} to 10^{-10} Ci/liter (ref. 38, p. 226). Seawater containing a tritium concentration of 3×10^{-2} Ci/liter was shown to affect the germination of spores of *Padina japonica* and the subsequent growth of the embryos

(*50*). The biological effects of effluent from production reactors at the Hanford plant have been monitored for more than 20 years by rearing salmonids in diluted effluent. No effects were observed at levels up to 6% effluent which is far above existing levels in the river (*51-53*).

D. Internal Emitters

Only ^{32}P and ^{65}Zn have been found to accumulate in significant amounts in fish flesh as a result of effluent from the Hanford plants (*54*). Studies were done in which varying levels of ^{32}P, ^{65}Zn and ^{90}Sr were fed daily to rainbow trout for 17 to 25 weeks (*55-57*). Levels at which no effects were observed are as follows: ^{32}P - 0.006 Ci/g fish/day; ^{65}Zn - 1.0; ^{90}Sr - 0.05; these levels are estimated to correspond to hundreds of rads total absorbed dose. Effects at higher levels included growth depression, mortality, and leukopenia.

The term "concentration factor" is commonly used to express the ratio of the concentration of a radionuclide in an aquatic organism to that in its ambient water. Tables of concentration factors are available for different radionuclides, different trophic levels and different species (ref. 38, p. 168). These data, although far from complete and adequate, may be helpful for predictive purposes and any assessments should take them into account. But they must be used with caution because the values depend upon many variables. Phytoplankton and zooplankton may show concentration factors in the order of 10^5 but values for other organisms are generally orders of magnitude.

E. Environmental Factors and Radiation Effects

Because nuclear and desalination plants could release heat and highly saline water, there has been interest in the interaction of these factors on response to radiation. As a rule, greater radiosensitivity is observed following temperature elevation during or after radiation exposure. Salinity also has an effect, which, however, cannot be simply generalized. It must be emphasized that any critical assessment should take into account to the extent possible the interactions of the environmental factors known to be important. These would include oxygen in addition to the above.

F. Radiation Effects on Populations

The major concern is with low-level radiation effects on populations and ecosystems in the aquatic environment rather than with effects on individuals. There are no data at the radiation levels of interest (levels associated with human population exposures of a few millerem per year); however, there are many high-level studies that do provide us with an important base-line. Controlled studies have been done on the effect of gamma radiation (25 to 75 R/hr for 19 hr/day) on *Daphnia* (*58*) and on the effect of repeated contamination with ^{32}P and ^{65}Zn (~7 - 30 μCi/liter) on the reproductive capacity of mass cultures of *Artemia* which were followed for eight years (*59, 60*). Large-scale environmental observations are available from weapons testing at Bikini and Eniwitok at the Pacific Proving Grounds (*38*, p. 232). Detailed studies have been made in the Irish Sea costal area adjacent to the Windscale reprocessing plant where annual exposures of 7300 mrads could be accumulated by certain fish and at White Oak Creek and White Oak Lake (Oak Ridge, Tenn.) where larvae have been exposed to dose rates of about 240,000 mrads/yr for over 22 years (38, pp. 234-5).

The major conclusion from all of these observations is exemplified by the studies at the Pacific Proving Grounds. This aquatic environment was exposed to intensely high radiation levels; despite initial large-scale destruction of life, the ecosystem was neither irreversibly nor irreparably damaged. After 25 years, life on the reefs has recovered and marine life has re-established itself. Individuals from unaffected areas have repopulated and occupied the reefs. Thus, if radionuclides are present in concentrations acceptable for man, it is difficult to conceive that damaging effects on aquatic systems could occur.

Thought needs to be given to any possible effects on aquatic resources of changes in fecundity and mortality. A prevailing view, based on field observation, is that generally the normal survival of eggs is so low that large increases in the mortality at the egg stage would have very little effect on the mortality rate of the species (*61*). This would hold for all highly fecund species.

It may be generalized that an accidental event involving large amounts of radioactivity would be local in nature and there would be repopulation and recovery of the ecosystem with time. On the other hand, planned releases that could be more widespread would involve radioactivity at such low levels that any effect on fecundity or mortality of fish stocks could not alter the fish population as a food resource. The planned release would take into account distribution and reconcentration factors and the radioactivity allowed to enter this ecosystem would be regulated so that the use of fish for food would not expose the human population in excess of acceptable standards.

IV. Soil - Plant Systems

Depending upon chemical behavior, the soil can be a sink in which the individual radionuclide may be stored with little chance of entering the biosphere; or the soil may act as a reservoir from which plants and organisms can be exposed for long time periods after the initial soil contamination. Exposure can occur from direct uptake, entry into surface, ground, or irrigation waters, or direct irradiation. The role of soil is assessed mainly in terms of the amounts of various radionuclides that occur naturally or have been added to soil and knowledge of their behavior in the soil environment.

A. Natural Radionuclides (*62-80*)

Although numerous natural radionuclides are known to exist in soil, almost all of the radioactivity is comprised of the following plus decay products: potassium -40, rubidium -87, thorium -232, uranium -235, uranium -238 (*70*). In addition, naturally occurring tritium and carbon-14 are of interest because of their ready entry into living organisms. The total amount of natural radioactivity in one square meter of soil to normal cultivation depth (about 200 kg) is usually between 5 and 10 microcuries. Exceptional soils may contain more than three times the average concentration of potassium and rubidium and more than ten times the average concentrations of thorium and uranium.

Among the decay products of thorium -232 and uranium -238 are the gases radon -220 and radon -222, respectively, of which a small fraction escapes to the atmosphere where they decay to form radionuclides of polonium and lead which gradually return to the soil as a natural fallout (*92*). These do not contribute appreciably to soil levels but do constitute a significant part of the plant content of lead 214, lead 212, lead 210, and polonium 210.

B. Radioactive Fallout (*81, 91*)

Radioactivity has been deposited upon the earth's surface from nuclear explosions — nuclear fission was predominant during the period 1958-60 and fusion during the period 1962-64. Soil levels of the long-lived fission products ^{90}Sr and ^{137}Cs have been well documented in the United States. Average levels of ^{90}Sr in soils increased from about 0.015 microcuries per square meter in 1958 to a maximum of 0.065 in 1967. The highest level found in the United States outside of the Nevada Test Site was 0.160 microcuries per square meter in a high rainfall area of western Washington (81, HASL 173). ^{137}Cs deposition is about 50% greater than that of ^{90}Sr. Maximum accumulations of moderate-lived fission products occurred in 1959; soil levels of ^{144}Ce, ^{106}Ru, and ^{95}Zr ranged from 0.40 to 0.74 microcuries per square meter (84) . In 1963, levels nearly as high were reached. There are no direct data on accumulations of short-lived nuclides in soil but estimates from milk levels indicate that deposits of ^{140}Ba and ^{131}I were about 1 microcurie per square meter in some areas of Utah in 1962. Soil levels of short-lived radionuclides are not contributors and have no relevance for human exposures via the food chain.

Levels of carbon -14 and tritium added to soils from fallout can only be estimated indirectly from air and rainfall concentrations. Carbon occurs in soils mainly in humus and carbonate minerals and the ^{14}C is added through incorporation of crop residues as fresh organic matter. However, this contribution is small, has not been capable of measurement, and is estimated to be of the order of 0.014 microcuries per square meter (*77*). Hydrogen occurs in soils in water and in humus. Based on rainfall analysis, tritium in wet soils may have reached 6 microcuries per square meter in 1963 (*93*). In peat soils, the humus could be a contributor of tritium but probably soil water is much more important.

Rainfall concentrations indicate maximum accumulations of 0.04 microcuries of ^{54}Mn and

0.2 microcuries of ^{55}Fe per square meter in 1963 or 1964.

C. Other Sources of Radiocontamination (*94-101*)

Soil contamination can occur from reactor effluents, reprocessing wastes, mining operations, and accidental releases. The pathway can be via the atmosphere, by irrigation or flooding of streams, or by seepage of contaminated ground water from radioactive waste disposal areas.

Experience from the reactor accident at Windscale, England, indicated that ^{131}I contamination, which did not involve the soil, was most important; initial depositions were estimated to be about 40 microcuries per square meter for ^{131}I and about 0.2 microcuries per square meter each of ^{89}Sr, ^{90}Sr, and ^{137}Cs in the surrounding area (*94*).

Data are available for levels of radionuclides in farm produce originating from irrigation water from the Columbia River below the Hanford reactors. Following are the average concentrations (pCi/liter) of the major radionuclides in the water from 1958 to 1965: ^{24}Na - 2000; ^{32}P - 200; ^{51}Cr - 5000; ^{65}Zn - 200; ^{76}As - 1000; ^{239}Np - 2000 (*102*). Only ^{32}P and ^{65}Zn were found in the milk and these at average concentrations of 700 and 500 pCi/liter respectively. The highest concentration of ^{32}P was 5700 pCi/liter in August 1964 following a period of unusually heavy irrigation.

Patterns of ground water flow and radionuclide movement in ground water have also been studied at Hanford. The ground water flow rate was about 1 mile per year requiring at least 15 years for movement from the Hanford disposal areas to the river. Most radionuclides moved only a few feet from the disposal site; only tritium, technetium -99, and ruthenium -106 were observed to move nearly as fast as the ground water (*131*).

Redistribution of wastes from uranium mining depends greatly on local geography and climate. In some instances, the major method of redistribution has been by wind (*103*), in others by solution and transport of particles in streams (*95*).

D. Redistribution of Radionuclides (*104-146*)

Radionuclides in or upon the soil can be redistributed or recycled by processes of erosion, sedimentation, desorption, leaching, and irrigation.

Redistribution through erosion and sedimentation may be very great in sloping areas, depending on average slope and amount of runoff. For example, more than half of the fallout ^{90}Sr on cultivated one-acre watersheds with from 10 to 15% slope had been eroded away in 1960 (*133*). Individual storm runoff has been shown to carry a few percent of fallout being deposited in the current storm with radionuclide loss being roughly correlated with water runoff (*134*). Estimates of ^{90}Sr movement from major river basins have been calculated from flow data and ^{90}Sr concentrations in many locations (*147*). For the period 1958 to 1967, the amounts moved ranged from 0.1 to 10 mCi/km^2 of drainage area as compared with accumulated deposits of 50 to 100 mCi/km^2 in 1967. Thus, as a rough generalization, from 5 to 10 percent of the ^{90}Sr fallout was removed in areas with the greatest runoff (mountain and coastal regions), less than 5 percent in mid-sections of the country, and less than 1% in arid sections.

Deposition of sediment occurs in reservoirs and quiet stretches of streams, the extent depending upon particle size and holding times. It has been estimated that in the United States about one-fourth of the sediment produced is trapped in man-made reservoirs.

Desorption of radionuclides from soils follows the principles of ion exchange, the important factors being the properties of the radionuclide, the composition of the displacing solution and the exchange capacity of the soil. Generally, monovalent ions are most easily displaced, then divalent and trivalent ions. Anions are more easily displaced than cations because the charges on soil particles are predominantly negative. Downward movement in soils can occur by leaching or particle movement. Field studies in 1966 showed that 95% or more of the ^{90}Sr and ^{137}Cs were in the top six inches of soil except where there had been mechanical movement of particles (*81*, HASL 183). Only tritium, technetium 99 and ruthenium 106 have been observed to move with ground water. Iodide also moves through soils that are low in organic matter.

Irrigation may be an important process in the recycling of radionuclides from water to terrestrial food chains. In furrow irrigation, plants can become contaminated by uptake of radionuclides added to the soil; in sprinkler irrigation there is the additional direct contamination from the wetting of foliage. Limited experimentation leads to the generalization that sprinkler irrigation produces vegetation with about the same concentrations of ^{90}Sr and ^{137}Cs as in the irrigation water (*146*). Long continued use of contaminated irrigation can result in the accumulation of long-lived radionuclides in the soil. Estimates have been made that the concentration of ^{90}Sr in a green crop on a fresh weight basis could reach 20 times the concentration in irrigation water after a few decades of irrigation.

E. Radiation Effects in Soils (*107-113, 148-157*)

Gamma-emitting radionuclides spread on the soil surface irradiate rather uniformly any organisms living above the surface. However, the radiation dose decreases sharply with depth unless the radionuclides are mixed in the soil. For example, the gamma dose from fresh fission products on the soil surface would decrease about 100 fold for each meter depth in the soil (*156*). Beta rays penetrate much shorter distances, being appreciably absorbed by a leaf or plant stem and almost completely by 5 mm of soil, depending upon their energy. Thus, the distribution of beta-emitting radionuclides on soil or plant surfaces is critical in determining radiation exposure (*153*). Insects that feed or nest in leaf whorls or flower cups and some sensitive plant tissues such as actively growing meristems may be exposed to much more beta radiation than would be expected from the general intensity of gamma radiation in the area. Alpha rays present little external radiation hazard to higher plants and animals; specific hazards to single-celled organisms are largely unevaluated.

Lower forms of life are generally more resistant to radiation than are the higher forms. For example, 10,000 rads would kill many higher plants or animals upon or within the soil which might release inorganic nutrients and stimulate growth of fungi and bacteria. Doses greater than 50,000 rads reduce the microbial population in soils and could result in selective killing of different bacterial groups (*157*). Radiation doses less than 1000 rads would probably have negligible chemical, physical, or biological effects upon soils. The most sensitive chemical effects appear to be increases in nitrate and ammonium concentrations in soil solution observed at exposures of about 1500 rads (*148*).

From the standpoint of external irradiation, environmental releases of radioactivity controlled so that crops and animal produce would be acceptable to man are not at all likely to produce observable or significant long-term genetic changes in the organisms that reside in or on the soil. Any effects would require extreme contamination such as might result from close-in fallout from nuclear explosions or utilization of areas for high-level waste disposal.

F. Radionuclide Entry into Plants and Radiation Effects (*113, 158-172*)

Plants may become contaminated by absorption through roots or through above-ground parts including leaves, stems and branches, flowers and fruit (*113*). Root absorption depends largely upon soil processes involving ionic form, pH, exchange capacity, moisture, and temperature. Some elements are strongly concentrated by plants (e.g. K, Rb, P, Na); some slightly concentrated (Ca, Sr, Mn, Zn); some not concentrated (Ba, Ra, Co); and some almost excluded (Cs, Fe, Ru, Sc, Y, Ce, Pb, U, Th, Pu) (*154*). Lowering pH values generally increases cation uptake and decreases anion uptake. Increasing exchange capacity tends to decrease both cation and anion uptake. Highly organic soils permit increased Cs uptake as compared to mineral soils. Flooding of soils tends to increase the uptake of Cs and I. Legumes have a tendency to absorb more alkaline earths than alkali cations but the reverse is true for grasses. Brazil nuts are effective accumulators of barium and rare earths with relatively high levels of alpha emitting nuclides.

Direct contamination of foliage leads to a much higher radionuclide content than uptake through roots when the fallout rate is high. Three mechanisms of direct contamination have been recognized: foliar contamination which is retention and absorption through the leaves; floral contamination, which is entrapment and absorption in inflorescends; and plant-base absorption, which is entry into the basal tissues of shoots or superficial roots by material initially lodged on them or washed down by rain from the foliage. Material is deposited on plants by dust or other particulate matter, precipitation or sprays. Retention depends upon such factors as intensity and amount of precipitation, wind speed, particle size and density, wettability of leaves, leaf type and age, and thickness and continuity of the cuticle. To the extent that radionuclides are water-soluble, they may be absorbed through the leaves or basal tissues following much the same relationships described previously for root absorption. Once absorbed, processes of translocation influence distribution within the plant.

Metabolites accumulate in certain plant parts depending upon the metabolism of the substance and the physiological stage of development. For example, calcium and strontium are found in cell wall materials and are not readily retranslocated to other parts. Elements such as potassium, phosphorus, sodium, rubidium and cesium are freely mobile. Phosphorus is accumulated in areas of high metabolic activity such as root tips, buds, flowers and developing leaves. Carbohydrates are transferred from leaves, where they are manufactured, to areas of active growth and metabolism; this behavior would govern the distribution of contaminating radioactive carbon compounds. In general, substances are preferentially translocated to the plant organ or part that is developing at the particular time. This could be important especially if contamination occurs simultaneously with development of a specialized part that is utilized for food.

Substances in plants are returned to soil by death and decay, leaching by rain or dew, exudation, and volatilization of gaseous substances from plants.

Much work has been done on radiocontamination of grazing lands because of the importance of pasture as a route of exposure of man. Both direct contamination and absorption from the soil are important. Perhaps the primary factor in soil uptake is the distribution of the nuclide in soil. Most pasture grasses obtain their nutrients from the top few inches of soil, and in humid regions have shallow root systems; thus, the passage of time may remove contaminants from the rooting zone or otherwise reduce their accessibility. It appears that the rate of reduction of uptake of ^{90}Sr from soil is about 13-14% annually (*197*). The relative contribution of the soil ^{90}Sr to milk was reported in 1965 to vary from about 20 to 50% in different years, being greatest in times of low fallout and making only a minor contribution in years of relatively high fallout.

In temperate regions, mineral soils, which bind ^{137}Cs, predominate. Studies have shown that only about 0.01% of ^{137}Cs artifically applied to an average bluegrass pasture was transferred from soil to grass (*105*). Experience with organic soils in Florida indicated a generally enhanced uptake from the soil in this region (*207*).

Although not a pasture plant, lichen is of considerable interest since, in arctic and subarctic regions, it provides the main source of winter grazing for reindeer and caribou. Lichen has no root system; all absorption occurs from its mycelial surface. The surface area of a typical lichen is about 10 times that of a typical grass. Accumulation of deposited material is promoted by the long growth period (tens of years) and the fact that some nuclides can be translocated within the plant. The young green living top which is grazed can remain contaminated for long time periods after contamination because of translocation of nuclides from older parts. It is reported that up to 95% of deposited ^{137}Cs can be retained by lichen with a biological half-life in the plant of up to 17 years (*106*).

There are little or no data on the effects of low level chronic irradiation of plants. *Lilium* and *Tradescantia* were affected by 30 to 40 R per day whereas plants such as gladiolus required up to 9000 R per day before extensive damage was noted. Conifers such as pines and Taxus were affected at about 2 R per day (*172*). Chronic effects have been seen in oak trees exposed for 10 years at about 7 R per day (*170*).

Generally speaking, flower parts and meristematic areas are much more sensitive to irradiation than are leaves, stems, and roots. Plants with low chromosome numbers and small nuclear volumes are more radiosensitive than are plants with high chromosome numbers (including polyploids) and larger nuclear volumes. In accordance with the general pattern, it is difficult to conceive of significant harm to plant populations at radiation exposures that could occur under conditions which were acceptable to man.

V. Animals and Animal Products

It is difficult to quantify or define the effects of environmental radiocontamination upon animal populations in their natural habitats. The most useful approach seems to be to compare risks to animal populations with those to man in the same environmental situation; this we have attempted to do. In addition, we have summarized the present status with regard to assessment of radiation doses via milk, meat, and eggs, because these animal products are a primary route of transfer of environmental contaminants to man. A detailed review has recently been published that deals with the transfer of radioactive material from the terrestrial environment to animals and man (*173*).

A. Relative Radiosensitivities

A scale of relative lethal response of the adults of a wide variety of species can be constructed from the literature (*174*). Invertebrates are found to be more resistant than vertebrates with insects and mollusks, for example, being able to survive kilorad exposures. Among the vertebrates, mammals are somewhat more radiosensitive than birds, fish, amphibia, or reptile. Published values for the LD 50/30 of mammals following whole-body x- or gamma radiation range from about 150 rad (sheep, burro) to 1500 rad (desert mice) with that for man placed tentatively at 225-270 rad (*175*). Fewer data are available on the response of eggs, which are generally more sensitive than adults; however, it appears to be a reasonable assumption that relative susceptibilities among species can be ranked in the same order as that of adults. The conclusion can therefore be drawn that if exposed to the same acute radiation dose no animal species would be at very much greater risk than man.

The primary concern in the context of peacetime environmental contamination is with exposures well below the lethal range and particularly with continuous exposures at low rates. Under these conditions, the effects on animals are expected to be qualitatively similar to those on man as described in detail in later chapters; these include genetic effects and somatic effects comprised of malignant disease, cataracts, skin damage, non-specific aging, effects on growth and development, and impaired fertility. It must be remembered that animals in their natural habitat do not usually attain more than a fraction of their potential lifespan, and under economic domestication are not usually retained beyond their reproductive lifespan. Thus, of all of the effects catalogued above, only impaired fertility may be of significance for the perpetuation of animal populations.

Both male and female germ cells of mammals are radiosensitive. On the basis of experiments with mice and dogs, observable effects on fertility would not be expected at exposure rates less than tens of rads per year (*176-178*). However, Russian studies have reported sterility in young male tundra voles (*Microtus oeconomus*) trapped from areas where the uranium-radium content of the soil causes exposures up to 70 R per year (*179*).

Thus, the application of existing population dose limits (0.17 rem average per year) across all animal populations would be expected to have an imperceptible impact upon them.

B. Routes of Exposure of Animal Populations

Releases to the atmosphere probably have the widest potential consequences. External radiation from an airborne cloud and inhalation can present transient hazards but the main source of external exposure is likely to be materials deposited on or in soil. The whole-body radiation dose to animals living in close proximity to or burrowing in soil would be perhaps ten times greater than the average dose to man, especially from beta ray contributions. Inhalation and ingestion via drinking water are rarely major routes of entry of radiocontaminants into the animal body. For a given contamination of air and water, it appears that animals are at no greater risk than man.

The major route of exposure of contaminating radionuclides for animals and man is through food. Under conditions of surface contamination of plant material relatively short-lived nuclides can be ingested in considerable amounts depending largely upon the morphology of the foliage as described in the previous section. Uptake by roots from the soil presents a continuing source of contamination to plant-eating species.

Ruminants are of particular importance; in their natural habitat, they either graze grass (sheep, cattle), or lichen (reindeer, caribou), or browse upon trees or shrubs (deer, some antelope, giraffe). They are most efficient as gatherers of surface contamination. For example, it is estimated that a cow at pasture consumes daily airborne contaminant equivalent to that deposited on 20 m^2 of ground, as contrasted to a value of 10 cm^2 for man representing daily consumption of green vegetables (*173, 180*). In ruminants, the unabsorbed ingesta constitutes an important source of internal exposure, particularly to the female gonads. It is estimated that the whole body exposure from mixed fission products ingested by a grazing cow from a nuclear detonation would approximate the external exposure from material on the ground surface. Nevertheless, it can be demonstrated that the consumption of animal products by man is limiting to man rather than any hazard to the animal. It has been calculated that if cows were to consume ^{131}I, ^{90}Sr, and ^{137}Cs at levels that would produce minimal pathological changes, the dose rate to children consuming fresh milk from them would be about 400 rem/yr to the thyroid, 180 rem/yr to bone, and 170 rem/yr to the whole body respectively (*113*).

During passage through a food chain, there can be progressive increases or decreases in concentration. Most elements decrease as they pass through the plant-herbivore-carnivore trophic levels. A few are concentrated, notably sodium in invertebrates and cesium in mammals. However, in mammals concentration factors are relatively small. Ninefold increases in ^{137}Cs have been reported through the plant-mule deer-cougar chain (*181*); fourfold increases in the lichen-caribou-wolf chain (*182*); and threefold increases in going from food to the human body (*183, 188*). Because man derives contaminating radionuclides from both plant and animal products, and because concentration factors are relatively small, the concentrations in mammalian predators would not be expected to differ from those in man by a large factor.

C. Animal Products as Sources of Human Exposure

Exposure of man from environmental radiocontamination arises mainly from contaminated food, agricultural crops, and animal produce. In the western world, milk has proven to be the primary vehicle. In addition, meat, poultry, and eggs are a potential source.

1. *Milk and Milk Products*

Most of the work on transfer of nuclides to milk has been confined to isotopes of iodine, strontium, and cesium. A frequently used parameter is the "transfer coefficient" which is the percentage of the daily intake transferred to each liter of milk under steady-state conditions. Milk concentrations are also expressed in terms of concentrations in cut herbage or amount of nuclide per unit area of herbage. Use of area as a basis stems from the observation that the area from which a grazing cow obtains its daily intake is relatively more constant than the quantity of herbage consumed. In the case of strontium, the results are often expressed as "observed ratios" which denote the comparative behavior of strontium and calcium (*184*).

Average transfer coefficients for ^{131}I determined for cows under laboratory conditions range from 0.5 to 1.0 percent of daily intake per liter of milk (*113*). Values from field trials have ranged from 0.12 to 2.4, the large variance arising primarily from differences in physical properties of fallout and in physiology of the animals (*185*). Calculations have indicated that continuous grazing of cows on pasture carrying 1 μCi of $^{131}I/m^2$ would lead to a milk concentration of about 0.2 μCi/liter: a ratio of 5:1. (*186*). Field trials and also the experience of the Windscale accident have indicated that an average ratio of 10:1 would be more appropriate (*187*).

Numerous studies have been done with ^{90}Sr (*113, 184*). An average value of 0.08 has been determined under laboratory conditions for the transfer coefficient of ^{90}Sr to cow's milk. Under field conditions, values from 0.05 to 0.22 have been reported. However, the transfer coefficient is dependent upon dietary calcium and it is more meaningful to express results in terms of Sr/Ca ratios in diets and milk (OR milk/diet = ^{90}Sr/Ca in milk ÷ ^{90}Sr/Ca in diet as measured at steady state). OR milk/diet values usually fall in the range of 0.08 to 0.16. Lower values have been reported in the literature but usually can be shown to be in error because the ^{90}Sr/Ca of diet did not reflect the total dietary intake or because account was not taken of the contribution to milk from skeletal stores of strontium and calcium.

A representative average value for the transfer coefficient of ^{137}Cs to cow's milk is 1.2 but field values have been reported as low as 0.25 (*113, 188*). Low values are thought to be due to the binding of ^{137}Cs on clay particles associated with hay or by adsorption in the rumen contents (*188*). Data on transfer coefficients for other elements are scarce but some ranges can be indicated (*173*): 1 to 4-Na, Zn, K; 0.1 to 1 - Ca, Fe, Co; 0.01 to 0.1 - Te, Ba, W, Po, Ra, U. The small amounts of very poorly absorbed elements (e.g. ^{144}Ce, ^{239}Pu) found in milk are thought to occur from fecal contamination (*189*).

Limited studies have been done on the transfer of ^{131}I, ^{90}Sr, and ^{137}Cs to milk products (*190-192*). From 0.4 to 2.7 percent of ^{131}I in the original milk has been found per gram of skim milk, cream, butter, and cheese. In assessment of potential exposure from ^{131}I in such products, the time delay in consumption permitting radioactive decay must be taken in account. Relative concentrations of ^{90}Sr in butter, cottage cheese, and cheddar cheese following *in vivo* contamination of milk have been reported as 0.07, 6.8 and 0.34 respectively. Since the distribution of strontium follows that of calcium in milk products there is nothing to be gained by substituting cheese for milk as a source of calcium in the human diet. For ^{137}Cs relative concentrations in butter vary from 0.03 to 0.11, in fresh cheese from 1.3 to 6.2, and cheddar cheese from 0.6 to 1.4.

Considerable attention has been given to the prediction of milk levels following pasture contamination. The objectives are to help in planning appropriate emergency measures following an uncontrolled release or to aid in the design of installations that release radioactivity under controlled conditions. These models fall into three categories: (a) semiempirical, based on field observations of overall transfer (*193-197*); (b) empirical, based on derived data for transfer from diet to milk, and assumptions as to amount of herbage grazed, proportion of deposited material retained on herbage, its rate of loss from herbage, and biological availability (*198-201*); (c) sophisticated, attempting to take into account seasonal variations in feeding practices and pasture conditions (*202*). For accurate estimations, it is emphasized that there must be a field study at the time and place of contamination. Reliable models have been described for predicting the total intake of ^{131}I and ^{137}Cs by an average individual from knowledge of the milk level at a known time after a contaminating event (*203-206*).

2. *Meat*

The transfer of ^{131}I to muscle tissue in terms of percentage of daily intake per kilogram has been reported as 0.15 for the cow and 3 for the sheep. Values for ^{137}Cs are: cow-4; sheep-8; goat-20; swine-26. For ^{90}Sr, values of OR body/diet range from 0.18 to 0.24 for the above species. Tissues other than muscle, such as liver and kidney, may tend to have higher levels of certain nuclides. Generally speaking, meat is not an important contributor of ^{131}I and ^{90}Sr to the human diet. Meat is estimated to contribute from 30% to 40% of the ^{137}Cs in the average U.S. diet. (See 113 and 173 for reviews of deposition in meat).

In parts of Florida, a combination of high milk and beef levels of ^{137}Cs have led to body burdens in the human population 2 to 3 times higher than those reported elsewhere in the coterminous U.S. during the same time period (*207, 208*). Under some circumstances, meat from wild ruminants may have higher levels than from domestic stock. Mule deer from north-central Colorado which are primarily browsers, had ^{144}Ce, ^{137}Cs, ^{54}Mn and ^{106}Ru in their livers and a muscle concentration of ^{137}Cs 5 to 13 times that reported for beef and pork (*209*).

In arctic and sub-arctic regions meat is a particularly important contributor to human dietary intake of radiocontamination. This is because of heavy surface contamination of slow growing lichen, dependence of grazing animals upon lichen for food in winter months, and high consumption of reindeer or caribou meat by the population. It has been estimated that animals feeding on lichen would have a

489-797 O - 72 - 4

daily intake of contaminating material 5 to 10 times higher than if they were feeding on green plants (*210, 211*). Although ^{137}Cs is the radionuclide contributing the largest radiation dose to these populations (estimated to reach an order of 200 mrad/yr) a number of others have also been detected in caribou flesh including ^{22}Na, ^{40}K, ^{54}Mn, ^{55}Fe, ^{60}Co, ^{106}Ru, ^{110m}Ag, ^{125}Sb, ^{134}Cs, ^{210}Pb, ^{210}Po, and ^{228}Th.

3. Poultry

Poultry are generally reared under shelter and only relatively long-lived nuclides in stored feed are likely to present any problem. However, hens kept on free range could be a source of some short-lived radionuclides. For example, following the Windscale accident, eggs from such hens were judged next to milk as a potential source of ^{131}I, the activity per egg being about one-twentieth that per liter of milk (*212*). ^{137}Cs is transferred effectively to eggs and muscle tissue whereas ^{90}Sr is primarily sequestered in the eggshell (*213*).

VI. Summary — An Ecological Approach

In general terms, man's welfare depends upon the long-range quality of his total environment. Substances removed or added in large enough amounts can lead to imbalance or disorder of a life support system that is the result of evolutionary development over the ages. Within recent years, many thousands of waste products from man's agricultural, industrial, and domestic activities have been poured into the natural environment. There they may be stored, moved, accumulated, or dispersed, finally reaching equilibrium positions with effects apparent either at the time of contamination or much delayed depending on ecological behavior. These pollutants first were recognized to affect adversely man's agricultural and industrial base but within the past decade there has been increased sensitivity to direct effects on man himself.

It is important to examine the release of radioactivity to see if ecological considerations have been overlooked as for example in the case of DDT. For many years, DDT was judged to be under control by regulatory agencies, for its effects were evaluated primarily in terms of the target organisms. Many years were required before the movement of DDT in the environment emerged to a point where it became of ecological concern. Radionuclides, just as noxious chemicals, can be stored, moved, and/or concentrated within various food chains and webs, with years and decades required before attainment of their ultimate distribution and expression of effects on sensitive organisms, including man.

However, there are many reasons why the situation with regard to radioactivity differs from that of pesticides and other chemical pollutants. One set of reasons involves regulation and use: (a) release of radioactivity has always been under primarily governmental control or regulation; (b) the amounts released have been relatively small as by-products mainly of nuclear testing, with no intent to produce effects on target organisms; (c) the possible hazards of radiation were recognized prior to environmental radiocontamination and large research efforts have been under way since then, especially on the biological effects of radiation and the details of food chains whereby radionuclides reach the diet of man; and (d) regulation of possible population exposures was promulgated in order to protect individual human beings. The other set of reasons involves biological effects. Evidence to-date indicates that probably no other living organisms are very much more radiosensitive than man so that if man as an individual is protected, then other organisms as populations would be most unlikely to suffer harm. In fact, it is very difficult if not impossible to detect any effects of radionuclides in the environment even at concentrations much higher than the minimum established by regulation agencies. Therefore, the significant ecological aspect in regard to radionuclides is to determine the pathways, rates, and concentrations as an essential measure of understanding their potential route to man through natural systems, which is quite different from the direct route of the traditional food chain e.g. grass-cow-man.

With the increased use of nuclear energy by man, it is only prudent, despite the improbability of direct effects, that ecological considerations should be improved and strengthened. Where radioactivity is released to the biosphere, there should be programs adequate to answer the following: (a) how much, where, and what type of radioactivity is released; (b) how are these materials moved through the environment; (c) where are they concentrated in natural systems; (d) how long might it take for them to move through these systems to a position of contact with man; (e) what is their effect on the environment itself; (f) how can this information be used as an early warning system to prevent potential problems from developing?

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Chapter V

GENETIC EFFECTS OF IONIZING RADIATION

I. Introduction and Brief History 42
  A. Historical Basis for Radiation Protection Guides for the General Population 42
  B. Early Genetic Risk Estimates 42
II. The Present Situation 44
  A. How Has the Problem Changed Since 1956 44
  B. What Has Been Learned Since the 1956 Report 44
III. What Kind of Genetic Damage Does Radiation Cause? 46
IV. Could an Increased Mutation Rate Possibly Be Beneficial? 48
V. Sources of Genetically Significant Radiation Exposure 49
VI. Risks Versus Benefits 51
VII. Methods of Estimating the Genetic Risks from Radiation 51
VIII. Risk Estimates 51
  A. The Risk Relative to That From Natural Background Radiation 51
  B. Risk Estimates for Specific Genetic Conditions 52
  C. Risk Relative to Current Incidence of Serious Disabilities .. 55
  D. Estimation of the Cost in Terms of Ill-Health 56
IX. Discussion 57
X. Summary and Conclusion 58

Appendices to Chapter V

  Explanatory Notes 60
  References 70

Chapter V

GENETIC EFFECTS OF IONIZING RADIATION

I. Introduction and Brief History

This chapter reviews briefly the information now available on the genetic risk to the human population from low levels of ionizing radiation and gives the Subcommittee's conclusions and recommendations. Supporting evidence and further information are given in a series of Explanatory Notes.

Our task was made much easier by the voluminous reports and extensive bibliographies prepared by the United Nations Scientific Committee on the Effects of Atomic Radiation (See Explanatory Note 1).

A. The Historical Basis for Radiation Protection Guides for the General Population

Although the discovery that radiation can cause mutations was reported by H. J. Muller in 1927, it was not until after World War II that genetic risks to the population were regarded as a major factor in determining maximum permissible doses. The emphasis instead had been on the protection of the individual who, for occupational or other reasons, might receive a radiation exposure that would be harmful to himself.

In 1956, the National Academy of Sciences - National Research Council Committee on the Biological Effects of Atomic Radiation (the BEAR Committee) introduced a new concept, the regulation of the over-all average dose to the population. Because of the genetic risk to future generations, the BEAR Genetics Committee recommended that man-made radiation be kept at such a level that the *average* individual exposure be less than 10 R (roentgens) before the mean age of reproduction, a period of time taken to be 30 years. Simultaneously, a report with a similar recommendation was issued by the British Medical Research Council. The 10 R numerical limitation was accepted by the National Committee of Radiation Protection (NCRP) and included in its 1957 recommendation. The present Radiation Protection Guides for the general population grew out of these recommendations (See Explanatory Note 2).

The BEAR Genetics Committee included medical radiation in its recommendations, the genetically significant medical dose (65 GSD) (prereproductive gonad exposure) at that time being estimated to be about half of the recommended 10 R limit. The Federal Radiation Council did not include medical radiation and, therefore, took 5 R as the 30-year limit for the population average in the Radiation Protection Guides. This is 0.17 R per year, or 170 milliroentgens, the value now in effect. There is at present no stated limitation on population exposure from medical practice.

The Radiation Protection Guides are stated in rems rather than roentgens, since the rem takes into account differences in biological effectiveness of different kinds of radiation. We shall also use rems and millirems as the units of our discussion, and thereby assume that when radiations of different biological effectiveness are used the exposures have been converted into roentgen equivalents.

B. Early Genetic Risk Estimates

The 1956 Genetics report relied mainly on data from *Drosophila* and the laboratory mouse, as there were almost no relevant human data. According to the BEAR report, "the best one can do is to use the excellent information on such lower forms as fruit flies, the emerging information for mice, the few sparse data we have for man. . .and then use the kind of biological judgment which has, after all, been so generally successful in interrelating the properties of forms of life which superficially appear so unlike but which turn out to be so remarkably similar in their basis aspects."

The general principles that guided the committee at that time were: (1) Mutations, spontaneous or induced, are usually harmful; thus, the harm from an increased mutation rate greatly outweighs any possible benefit. (2) Any dose of radiation, however small, that reaches the reproductive cells entails some genetic risk. (3) The number of mutations produced is proportional to the dose, so that linear extrapolation from high dose data provides a valid estimate of the low-dose effects. (4) The effect is independent of the rate at which the radiation is delivered and of the spacing between exposures. The last of these principles has turned out to be incorrect, as will be discussed later.

The BEAR Committee estimated that the amount of radiation required to produce a mutation rate equal to that which occurs spontaneously (a "doubling dose") was almost surely between 5 R and 150 R and probably between 30 and 80 R. It also assumed that about 2 percent of all live-born children are or will be seriously affected by defects with "a simple genetic origin." Under the assumption that for this fraction of human defects the incidence is proportional to the mutation rate, the effect at equilibrium after a continuing exposure to the recommended 10 R limit of radiation per generation was computed. Taking 40 R as a reasonable value for the doubling dose, the BEAR Committee calculated that 10 R per generation continued indefinitely would lead to about 5,000 new instances of "tangible inherited defects" per million births, with about one-tenth this number in the first generation after radiation begins.

The BEAR Committee also estimated the total number of mutations which would be produced at all gene loci by 10 R of radiation. The principles listed above made these calculations relatively simple. The number of mutations produced is (the number of genes in the population) x (the dose) x (the mutation rate per gene per unit dose). For the last quantity, mouse data were available. But there was no evidence from any mammal as to the number of genes per cell. For this, the Committee used *Drosophila* data, dividing the total mutation rate by that for individual genes. So the estimates of the number of mutations induced were for a hypothetical organism whose mutation rate per gene is that of the mouse and whose gene number is that of *Drosophila* (See Explanatory Note 3).

The Committee then used the principle that each harmful mutant gene is eventually eliminated from the population and that this occurs by reduced viability or fertility. Thus, in a statistical sense each new mutant gene, in a population of stable size, must eventually be balanced by a gene extinction. This extinction occurs through pre-reproductive death or reduced fertility. The BEAR Committee was divided as to the usefulness of this kind of calculation. It was noted that the death of an early embryo is much less traumatic than the death of a child or adult and that the failure to reproduce cannot be equated to premature death in any tangible way. How is a single major defect to be judged in comparison with a number of minor risks? As stated in the report: "This kind of estimate is not a meaningful one to certain geneticists. Their principal reservation is doubtless a feeling that, hard as it is to to estimate numbers of mutants, it is much harder still, at the present state of knowledge, to translate this over into a recognizable statement of harm to individual persons. Also, they recognize that there is a risk involved in extrapolating from mouse and *Drosophila* to the human case." But the group concluded that "in spite of all the difficulties and complications and ranges in numerical estimates, the result is nevertheless very sobering."

Based on these estimates and other considerations which it regarded as germane, the BEAR Genetics Committee made two recommendations that are related to our present purposes:

"That for the present it be accepted as a uniform national standard that x-ray installations (medical and nonmedical), power installations, disposal of radioactive wastes, experimental installations, testing of weapons, and all other human controllable sources of radiation be so restricted that members of our general population shall not receive from such sources an average of more than 10 roentgens, in addition to background, of ionizing radiation as a total accumulated dose to the reproductive cells from conception to age 30."

"The previous recommendation should be reconsidered periodically with the view to keeping the reproductive cell dose at the lowest practicable level. If it is feasible to reduce medical exposures, industrial exposures, or both, the total should be reduced accordingly."

The present subcommittee concurs with this recommendation for periodic review and it is in this spirit that the present study has been undertaken.

II. The Present Situation

A. How Has the Problem Changed Since 1956?

There have been three major changes: (1) As discussed elsewhere, somatic as well as genetic risks must now be taken into consideration in the setting of radiation protection guides for the general population, (2) the potential sources of population exposure have changed somewhat, and (3) new genetic knowledge necessitates revision of some of the earlier ideas.

When this problem was evaluated earlier, in 1956, the chief source of man-made radiation, aside from medical uses, was fallout from the testing of nuclear explosives. Exposure from nuclear power plants, although it was discussed, was not yet an immediate concern. Now the situation is quite different. There is very limited atmospheric testing of nuclear explosives. In the future, there will probably be either no appreciable exposure from fallout, or the amount will be so staggering that any reasonable standard is breached. We are also faced with an energy problem. An expanding world population with ever-rising expectations for a higher standard of living, which implies more energy consumption, is confronted by dwindling supplies of accessible, economically feasible fossil fuels. There is, furthermore, increasing concern over pollution, and the fossil fuels are clearly major sources of atmospheric pollutants. Thus, not only does there appear to be a need for more energy, but the main alternative to atomic energy, fossil fuels, is accompanied by newly recognized health and other hazards of its own.

For the United States population in 1956, exposure from medical radiation was much greater than that from weapons testing or nuclear installations. The genetically significant exposure to radiation during a 30-year period at the rates estimated at that time were 3R from medical uses and 0.1 R from fallout, with no measurable exposure of the general public from the nuclear power industry. Technical developments have made it possible to reduce the amount of medical radiation per procedure without significant loss of diagnostic efficiency. Although the number of radiological examinations per capita has gone up, the average genetically significant dose from this source has not increased proportionately and may have been reduced. Data are given below (Section V).

It is important to stress that man-made radiation to which we are exposed is self-imposed by our demands for medical care and for energy. Furthermore, as mentioned above, alternatives to radiation also involve risks. Accordingly, all calculations of possible genetic consequences of ionizing radiation from nuclear power developments and from medical practice must be set against our needs and the risks of the alternatives. The risk-benefit equation is particularly hard to balance in the case of genetic risks, for those who receive the benefits and those who run the risk are not the same people—those at risk may be many generations in the future.

To summarize: The problem has not changed greatly since 1956, Medical radiation is still the major man-made contributor to the genetic risk. Nuclear power has become a reality and the radiation effect of this must be taken into account. Fallout from nuclear testing is reduced. We are much more aware of other kinds of environmental genetic risks. Yet, the difficulties still remain. Despite the new knowledge that will be discussed in the next section, the assessment of genetic risks in any meaningful quantitative terms is still very uncertain.

B. What Has Been Learned Since the 1956 Report?

Since 1956, our knowledge of genetics has been revolutionized. The chemical structure of the gene and the nature of the mutation process are now understood in great detail. The number of recognized genetic diseases has increased by more than four-fold. One disease after another is being understood in molecular and chemical terms. Human chromosomes can now be studied with great precision, whereas at the time of the first BEAR report not even the correct number of human chromosomes was known. Chromosome aberrations have been shown to be an important cause of human malformation and embryonic death. With such deep fundamental knowledge one might expect that estimation of radiation risks could now be made with considerable precision. Unfortunately, there are serious gaps in our knowledge. Most serious are: (1) almost complete absence of information on radiation-induced mutation in man; and (2) our inability to quantify the relation between an increased mutation rate and deleterious effects on human well-being.

Recent studies of radiation genetics have brought out new, and in some cases unexpected, complexities. As mentioned before, the principle of dose-rate independence has turned out to be wrong; it is now known that, for germ cell stages in the mouse that correspond to the human stages of the longest duration, radiation given at a very low rate or at widely spaced intervals produces fewer mutations than the same total dose given more rapidly. More mechanisms are now known by which radiation damage may be repaired in the cell. Furthermore, radiation effects differ among species, among strains of the same species, between the sexes, and among different cell stages (See Explanatory Note 4).

For these reasons, although we have much information not available to the writers of the 1956 BEAR Report, we cannot be any more certain than they were about quantitative assessments. A further difficulty is that, despite the increase in knowledge regarding the molecular nature of some chemically induced mutation processes, the molecular and cellular bases of genetic damage from ionizing radiation remain less well understood. Our knowledge is, therefore, insufficient to provide a strong theoretical basis for extrapolation from one biological system to another, and to man in particular. Nevertheless, in the absence of accurate human data we have no choice but to rely mainly on information from experimental animals.

Assessing the changes in our knowledge since 1956, we now ask: Are the earlier estimates of risk too high or too low in view of current information?

Several reasons suggest that the early risk assessments were, if anything, too high; others point in the opposite direction.

Among those new findings suggesting that the 1956 estimates were too high are the following. It is now known that exposure of male mice at low dose rates produces considerably fewer mutations per rem than the same dose at the high rates on which earlier estimates were based. It is also known that those stages in the male that are most susceptible to genetic damage, spermatids and spermatozoa, make up a very short part of the human reproductive life span. Furthermore, transmission of genetic damage in these sensitive cells can be prevented by postponement of conception until the mature sperm cells are derived from cells that were in a less sensitive stage at the time of the radiation. It is also known that the female mouse is, for most of her pre-reproductive life, much less sensitive to genetic effects of radiation than the male.

Another reason for suspecting that the earlier estimates may have been too high comes from empirical studies on the descendants of irradiated mice. These studies have revealed substantially fewer harmful effects than might have been expected from mutation rates for single genes. These animals were exposed to high doses of radiation for many generations (more than 40 in one case) and yet the offspring showed no demonstrable effect on viability, fertility, or growth, nor were there any detected abnormalities attributable to the radiation (See Explanatory Note 5).

On the other hand, there are reasons for thinking that the earlier estimates might have been too low. One is the increased realization that chromosome aberrations, structural and numerical, cause substantial genetic damage in man. A second reason is that, in addition to producing genetic effects by emitting radiation, radioactive isotopes may produce genetic changes as a direct result of the chemical change caused by transmutation. The latter, however, is believed to be a far smaller risk than the radiation effects (See Explanatory note 7). A third reason for thinking that the risk may have been underestimated in the earlier report comes from recent *Drosophila* studies. There is now strong evidence that mutations with very small effects occur with a much higher frequency than do those causing a conspicuous or lethal effect. That this class of mutations exists was realized earlier, but whereas at the time of the 1956 report they were estimated to occur with a frequency two or three times that of lethals it is now estimated that they are at least 10 times as frequent as lethals among spontaneous mutations. Furthermore, these mutations are expressed in the heterozygous state, so the effects would be manifest in the early generations after the occurrence of the mutation. There is supporting evidence for both of these conclusions from studies on bacteria and yeast. These conclusions are mitigated somewhat by *Drosophila* data suggesting that mutants with small effects expressed in the heterozygous state are less common, relative to lethals, among radiation-induced than among spontaneous mutants (See Explanatory Note 8).

The reasons for thinking that the earlier estimates of risk were too high are probably stronger than those for thinking that they were too low, especially if we consider the next half-dozen generations (which, of course, is much farther in the future than is ordinarily considered in policy determinations). The opinion of the Subcommittee is that the genetic risk estimates in 1956 were probably on the high and therefore conservative side, but there are far too many uncertainties to be dogmatic.

III. What Kind of Genetic Damage Does Radiation Cause?

The genetic effect of radiation is to produce gene mutations and chromosome aberrations. Some of the ways in which radiation produces such effects are given in Note 9. The effect of radiation on the well-being of the future population is a consequence of these changes. Because mutations and chromosome aberrations occur spontaneously, it follows that the consequences of radiation are not something new but rather an increase in frequency of various deleterious traits with which we are already beset. Since almost every aspect of the living organism is determined to some extent by its genes, the range of possible mutational effects encompasses virtually every aspect of our physical and mental well-being. The major exception is infectious disease, but even here inherited susceptibilities play a role.

Some results of genetic change are conspicuous, others are invisible; some are tragic, others so mild as to be trivial; some occur in the first generation following the gene or chromosome change, others are postponed tens or hundreds of generations into the future. Furthermore, most of the effects that are produced by mutation are mimicked by others, of nongenetic origin.

For all these reasons, radiation (or some other environmental agent) could be having an important effect on human well-being and yet this could go unnoticed. Even if the increase in mutation rate is large, the consequences are likely to be so heterogeneous in their nature, so diluted by space and time, and so obscured by similar conditions from other causes as to make it impossible to associate them with their cause. Only if all the affected persons in future generations could somehow be identified and brought together at one time and place could the total impact of the mutations be apparent.

One of the simplest categories of mutational damage includes those diseases and abnormalities that are caused by a single dominant mutation. The most recent compilation of McKusick (1) lists 415 such conditions with an additional 528 that are less well established. The collective incidence is very roughly one percent of persons born. Some examples are polydactyly (extra fingers and toes), achondroplasia (short-limbed dwarfism), Huntington's chorea (progressive involuntary movements and mental deterioration), one type of muscular dystrophy, several kinds of anemia, and retinoblastoma (an eye cancer). A mutation of this sort produces its effect in the first generation after its occurrence.

In contrast, recessive mutations, which require that the gene be present in duplicate in order to produce the trait, may not be expressed for many generations. The trait will appear only when two mutant genes are inherited, one from each of the two parents. Such individually mild effects may be collectively the cause of considerable human misery. However, this may not occur for a very long time. Indeed, the gene may be lost purely by chance in the Mendelian lottery, although this is balanced on the average by those mutants that increase in number by the same process. More important, there is good reason to think from animal experiments and from fragmentary human evidence that mutant genes are often lost from the population because of mild dominant effects on viability and fertility when the gene is heterozygous. Thus, there is a good chance that the gene will be eliminated from the population before it ever encounters another like itself.

McKusick lists 365 recessive diseases, plus 418 that are less certain. Some examples are phenylketonuria (or PKU, a form of mental deficiency), Tay Sach's disease (blindness and death in the first few years of life), sickle cell anemia and cystic fibrosis. These are fairly common and well known, but most recessive conditions listed in the book are very rare.

Recessive mutations located on the X chromosome are characterized by being expressed almost exclusively in males. Well known examples are hemophilia (failure of blood clotting), color blindness, and a severe form of muscular dystrophy. McKusick lists 86 well established and 64 probable conditions of this sort. Because the gene can be expressed in a single dose in males, which have only a single X chromosome, X-chromosome-linked recessive mutations are somewhat like dominant mutations on other chromosomes in that they are expressed soon after occurrence instead of being spread out over an extended time span.

Some of these dominant and recessive genes cause traits that we regard as normal, such as hair and eye color and blood groups. Others are not normal, but are so mild as to cause little concern. The great majority, however, cause diseases ranging from relatively mild to severe or even lethal. Most are so rare that they are known only to specialists. But, collectively, they are numerous enough that more than one percent of all children born will have a simply inherited disease causing an appreciable handicap.

Another type of easily classified genetic damage is due to chromosome aberrations. Errors in chromosome distribution can lead to an individual whose cells contain too many or too few chromosomes. The well known disease mongolism is caused by an extra representative of a specific chromosome (number 21). Most of the time, however, having too many or too few chromosomes leads to embryonic death; sometimes this is detected as a miscarriage, more often the death is so early as not to be detected at all. This kind of chromosome error is not thought to be strongly influenced by radiation, particularly at low doses.

Another source of chromosome imbalance is chromosome breakage. This is less frequent than the type of distribution error mentioned above among spontaneous instances of severe human anomalies. But ionizing radiation is much more effective at breaking chromosomes than in causing errors in chromosome distribution. The broken chromosomes may then reattach in various ways leading to rearranged gene orders, or they may be lost. The most frequently observed effect is a translocation—the exchange of parts between two (or more) chromosomes. Such a rearrangement is not harmful as long as both rearranged chromosomes, which among them have a normal gene content, are present. However, children of a person with such a "balanced" translocation often receive only one of the two rearranged chromosomes and their cells are therefore genetically unbalanced. The nature and the extent of the abnormality depends on the particular chromosome regions that are deficient or duplicated, and on the magnitude of the imbalance. The harm ranges from rather mild to very severe, even lethal. Typically, chromosome imbalance —if it does not produce embryonic death—leads to physical abnormalities, usually accompanied by mental deficiency.

What is most severe in one sense may not be the most tragic from the standpoint of human welfare. A chromosome aberration that causes early embryonic death may cause very little trauma, whereas the "milder" effect that permits the embryo to develop into a viable infant that is malformed and mentally retarded may be far more traumatic by any realistic measure of human suffering, both of the child and of his family.

Among translocations that are found among normal humans, the most common by far are Robertsonian translocations. These are fusions of two chromosomes, each having a spindle attachment at the end of the chromosome, to produce a single chromosome having the spindle attachment in the center. Such translocations have a population frequency of about 8 per 10,000. Usually the children are normal, since they inherit either the translocated pair or a pair of normal chromosomes.

However, they occasionally give rise to unbalanced gametes leading to embryonic death or to congenital anomalies. Radiation does not appear to be a major cause of these. Radiation-induced translocations are overwhelmingly of the reciprocal exchange type described in the paragraph above.

In addition to those abnormalities and diseases that are caused by mutation of a single gene or by chromosome breakage, there are other diseases to which gene variation undoubtedly contributes but where the inheritance is more complex. There is abundant evidence that there are inherited predispositions for many common conditions—for example, diabetes, schizophrenia, cancer, and mental retardation.

It is hard to assess the magnitude of the genetic component and it is even harder to assess what we want to know in the context of this report—the extent to which the disease incidence depends on the mutation rate. But, because this may well be the major way in which an increased mutation rate would exert a harmful effect, we shall use it as one basis for assessing radiation risks.

There is an additional class of mutation whose importance we don't know how to assess —those whose effects are so mild that they are not detected individually. As mentioned before, it is known in *Drosophila* that the most frequent of all mutations belong to a group that causes effects so mild that they can only be detected statistically in experiments involving large numbers. For example, a mutation might cause a one-percent reduction in the probability of surviving from the egg to the adult stage. Such a mutation is clearly impossible to detect in man, and very few mouse experiments are of a size to reveal it. We don't know what the other manifestations of such a mutant would be. (We cannot ask a Drosophila if it has a headache.) Perhaps the human counterparts of these mutations, in addition t[illegible]light reduction in life expectanc[illegible]ible for greater susceptibility to [illegible]red physical or mental vigor, or a slig[illegible]formation of some organ.

We cannot ignore such mild mutations as unimportant, because (1) if *Drosophila* is any indication, they are by far the most frequent class of mutations; and (2) being mild, with less effect on viability and fertility, they are more likely to be transmitted to future generations and continue to have their effect over a longer time, thereby affecting more persons. Thus, their impact is multiplied by the number of generations through which they persist; and taken over the whole period, and in conjunction with other mutants, their effect may be far from negligible (See Explanatory Note 8).

Despite a concern for this effect, we shall not attempt to estimate it quantitatively, for reasons to be discussed below. It is worth noting again, however, that in *Drosophila* the evidence is now good that this class of mutation is relatively less frequent among radiation induced mutations than among spontaneous mutations.

The contrast between genetic and somatic concerns is striking. The low-dose somatic effects that are most feared are cancer and leukemia. The evidence that high radiation doses have these effects is unequivocal. The evidence for low doses is less clear. For genetic effects of radiation, we have no direct evidence of human effects, even at high doses. Nevertheless, the animal evidence is so overwhelming that we have no doubt that humans are affected in much the same way. In contrast to somatic effects, where the concern is concentrated mainly on malignant disease, the genetic effects are on all kinds of conditions—for the spectrum of radiation-caused genetic disease is almost as wide as the spectrum from all other causes.

IV. Could an Increased Mutation Rate Possibly be Beneficial?

So far, we have been assuming that *any* increase in the mutation rate would be harmful to future generations. On the other hand, the theory of evolution assumes that mutations are the raw material on which evolutionary progress depends. The question is sometimes raised as to whether an increased mutation rate might be a good thing, increasing our evolutionary potential in a time of rapidly changing environment.

There are several answers. One is that we don't know what the optimum mutation rate for evolution is; probably there is no universal and simple answer. But, in any case, evolutionary theorists believe that in sexually reproducing species the rate of evolution is hardly ever, if ever, limited by the mutation rate. The difference between rapidly evolving and slowly evolving species is far more easily explained on the basis of such factors as availability of ecological opportunity and stability of the environment than by differences in mutation rate.

A second reason is purely empirical. In every species studied by geneticists, the overwhelming majority of mutations that have effects large enough to be readily observed are deleterious. The most conspicuous examples of beneficial mutations have been those that are discovered only in a drastically altered environment, such as DDT-resistant mutants in insects (which are beneficial from the insect's point of view). There are a large number of mutants whose effects are very slight and which are ordinarily not observed and studied; many of these have been revealed recently by sensitive chemical techniques. Among such mutants, there may be some whose effects on any body function are so slight as to produce no effect at all on the individual's well being. However, the existence of such possibly neutral mutations does not alter the general conclusion that, whenever there is an appreciable effect on the organism, the effect is almost always harmful. Natural selection preserves the rare beneficial mutants while eliminating the great majority of misfits.

We believe that a genetically diverse population is more to be desired than a uniform one, and this might be regarded as an argument for a high mutation rate. But the amount of genetic variability existing in the population is far greater than that which arises by mutation in a single generation. Furthermore, in some polymorphisms such as blood groups, hemoglobins, and serum proteins the entire variability may have arisen from a few mutant genes. If human mutation were to stop entirely, we should probably not notice any effect at all for many generations, except for some reduction in the incidence of severe dominant aberrations, among which are some of the most distressing diseases. The mutant genes now in the population arose in the past and have been pre-tested to some extent, the worst ones having been eliminated by natural selection. What we are saying is that there is ample genetic variability in the population for any evolutionary progress that is likely to occur in the foreseeable future. Indeed, some geneticists argue that for a long time to come the closer we can come to a mutation rate of zero, the better off we will be. Whether this is correct or not (and in any case lowering the spontaneous mutation rate is not now possible) the Subcommittee is convinced that any increase in the mutation rate will be harmful to future generations.

V. Sources of Genetically Significant Radiation Exposure

The sources of population exposure are treated in detail in Chapter III of this report. The main features are repeated in Table 1 for convenience of reference, together with the current Radiation Protection Guides for average population exposure.

The genetically significant dose (GSD) is an attempt to estimate the exposure that is relevant to mutation production. The gonad dose at each age and sex is weighted by the expected number of future children for a person of that age and sex. This is the procedure used in estimating the GSD from medical and dental radiation. For natural radiation, the GSD is assumed to be the same as the Gonad dose, since exposure is uniformly distributed over all ages. It is somewhat less than the whole body radiation because of shielding of the gonad by other body tissues. For fallout, occupational exposure, and nuclear power we have not attempted to convert these into gonad doses, since the amounts are so small. The occupational exposure is obtained by considering the total radiation received by those occupationally exposed, and treating this total as if it were uniformly distributed over the whole population. The genetically significant dose is probably considerably less than the 0.8 mrem in the table because of the age distribution of those who are occupationally exposed.

The estimates of exposure from nuclear power developments in the year 2000 are based on an assumed increase from 6000 megawatts in 1970 to 800,000 in 2000, along with corresponding increases in mining and fuel reprocessing. As mentioned in Chapter III, there is the further assumption that the radiation level at the site boundary is 5 mrem per year per reactor. It is important to emphasize, however, that no

Table 1. Sources of genetically significant radiation. Estimated average amounts taken from tables in Chapter III.

Source	mrem/year	
	Whole body exposure	Genetically significant exposure
Natural radiation		
Cosmic radiation	44	
Radionuclides in the body	18	
External gamma radiation	40	
Total	102	90
Man-made radiation		
Medical and dental	73	30-60
Fallout	4	
Occupational exposure	0.8	
Nuclear power (1970)	0.003	
Nuclear power (2000)	<1	
Radiation Protection Guide for man-made radiation (medical excluded to the general population (for reference)	170	

allowance has been made for failure to meet the expected levels of performance, nor for accidents or sabotage.

In the United States the genetically significant exposure from diagnostic radiation in 1964 was estimated to be 55 mrem per year. By 1970, the exposure was reduced to an estimated 36 mrem per year, of which about 2/3 is in males and 1/3 in females. The genetically significant exposure from therapeutic radiation is much less, being about 5 mrem per year. That from dental radiation is still less and may be considered negligible in comparison with diagnostic radiation.

We note that, despite recent reductions, medical radiation continues to be the largest man-made source of gonadal radiation. We believe that it is feasible to lower this exposure still more by such things as improved diagnostic equipment, image amplification, attention to gonadal shielding, rigorous adherence to operational standards, elimination of all medically unwarranted exposure, and better training of personnel.

It also appears to be technologically feasible to develop nuclear power, at least for the near future, with a genetic exposure that is a very small fraction of the natural background, and less than one percent of the present radiation protection guides.

Table 1 represents only average values for the population. There may be considerable variation about these averages. From the standpoint of estimating the overall genetic impact of radiation on future generations, the population average is the most important figure.

VI. Risks versus Benefits

It is not a part of the Subcommittee's assigned task to balance benefits against risks. Nonetheless, we should like to make some general remarks.

It is clear at the outset that an assessment of risk is useful for arriving at a rational decision only if it is compared to the benefits, or to the difficulty of reducing the risk. It goes without saying that if there were no benefits there would be no excuse for taking any avoidable risk whatsoever. Furthermore, if the risk can be decreased at an acceptable increase in cost, this should be done even though the benefit may heavily outweigh the risk.

The risk estimate is useful for answering three related questions:

(1) Do economic and social benefits associated with the radiation outweigh the genetic cost of the radiation?

(2) Do alternatives to the use of radiation also involve a risk, and if so is this risk greater or less than that of radiation?

(3) Are the costs of exposure reduction too great a price to pay for the reduced genetic risk?

We are fully aware that both the costs and benefits are difficult to measure with any precision and often they are expressed in units that are incommensurable. Yet even crude and uncertain estimates can often lead to a more rational policy than would be possible if no such assessments were available. It is with this philosophy that we proceed to discuss risk estimates.

VII. Methods of Estimating the Genetic Risks from Radiation

The task of the Committee is to: "(1) Review the scientific bases for the evaluation of risks at low levels of radiation exposures; (2) select the scientific basis it recommends the Environmental Protection Agency (EPA) to use; (3) make such estimates of risks as it deems scientifically appropriate; and (4) delineate the interpretations that can be attributed to the estimates."

From the earlier sections it is clear that, although we are beginning to get some information from direct human studies, we must still rely mainly on experimental animals—in particular the mouse—for quantitative data. We recommend the following general principles for risk estimation:

1. Use relevant data from all sources, but emphasize human data when feasible. In general, when data of comparable accuracy exist, place greater emphasis on organisms closest to man.

2. Use data from the lowest doses and dose-rates for which reliable data exist, as being more relevant to the usual conditions of human exposure.

3. Use simple linear interpolation between the lowest reliable dose data and the spontaneous or zero dose rate. In order to get any kind of precision from experiments of manageable size, it is necessary to use dosages much higher than are expected for the human population. Some mathematical assumption is necessary and the linear model, if not always correct, is likely to err on the safe side. (see Explanatory Note 10)

4. If cell stages differ in sensitivity, weight the data in accordance with the duration of the stage.

5. If the sexes differ in sensitivity, use the unweighted average of data for the two sexes.

The Subcommittee has considered various ways of estimating the genetic risk. Some, which were considered and rejected, are discussed later. The four ways that we have used are related to the kinds of diseases discussed in Section III. They are:

1. The risk relative to natural background radiation.
2. The risks for specific genetic conditions.
3. The risk for severe malformation and disease.
4. The risk in terms of over-all ill health.

Our view is that there are so many facets to the problem that several ways of estimating the risk are more useful than any single one in arriving at the best policy decisions.

VIII. Risk Estimates

We now present risk estimates made in the four ways listed above:

A. The Risk Relative to that from Natural Background Radiation

This is not really a risk estimate at all, but may nevertheless be useful as a policy guide.

As mentioned earlier, the natural level of radiation averages about 100 mrem per year. This varies considerably from one region to another, depending especially on the kinds of minerals present in the earth and on the altitude. A person who lives in a stone house may get more radiation than one who lives in a wooden house, because of the greater radioactivity of some rocks, such as granite. Likewise, a person who lives at a high altitude receives more radiation from cosmic rays. Exposure to man-made radiation near the level of background radiation will produce additional effects of a magnitude comparable to what man has experienced from this source throughout his entire history. Furthermore, since man-made radiations are not qualitatively different from natural radiation, they will not produce novel effects. These are particularly firm conclusions because they do not require any quantitative genetic information.

Another way of stating this is to note that the annual difference in natural radiation between a location in Louisiana and one in Colorado might be 100 mrem or more. Even a person who knows this probably doesn't take this difference into account in deciding to change his residence. We can regard man-made radiation levels of this magnitude as comparable to other risks that are often accepted.

The idea of using the background radiation level as a yardstick for setting standards is not new. The BEAR Committee had this in mind as one consideration in formulating its recommendations. It was specifically used by the Ad Hoc Committee of the National Committee on Radiation Protection and Measurements (NCRP) in its recommendations for limitations on the somatic radiation dose for the general population (2). The Committee recommended that "the population permissible dose for man-made radiation, excluding medical and dental sources, should not be larger than that due to natural background radiation, without a careful examination of the reasons for, and the expected benefits to society from, the larger dose."

To summarize: Our first recommendation is that the natural background radiation be used as a standard for comparison. If the genetically significant exposure is kept well below this amount, we are assured that the additional consequences will neither differ in kind from those which we have experienced throughout human history nor exceed them in quantity.

B. Risk Estimates for Specific Genetic Conditions

It seems most meaningful to compare the current incidence of specific genetic conditions to the expected increase from radiation. To do this, we first consider a convenient yardstick, the relative mutation risk per rem. This is the fraction by which the mutation rate would be increased by one rem of radiation. The reciprocal of this is the mutation rate-doubling dose, the dose required to produce as many mutations as occur naturally.

We estimate these quantitites as follows: In the absence of human data on radiation effects, we use data from the mouse. A chronic radiation dose to mouse spermatogonia produces about 0.5×10^{-7} recessive mutations per rem per gene. The reproductive cells of the female, for most of their lifetime, are very much less mutable than those in the male, even from acute irradiation. Furthermore, the germ cell stages in the female that have a high mutational sensitivity to acute irradiation, namely, the mature oocytes, give a very low mutation rate with chronic irradiation. Therefore, we take the average of the two sexes as 0.25×10^{-7} (See Explanatory Note 11). This may be too high, since the gene loci on which these studies were made were to some extent preselected for mutability; they would not be included in the study if they had not mutated at least once in the strains studied. Another reason for thinking that this may be too high is that in mice the rate of induction of dominant visible mutations is lower than that for recessives by at least an order of magnitude. Dominant mutations constitute a substantial part of the human genetic risk.

For the spontaneous rate, human data are available. The rates are variable. Many genes have mutation rates in the vicinity of 10^{-5} per gene per generation, but there is reason to believe that these are a nonrandom sample on the high side. We suspect that the true average rate is an order of magnitude less (See Explanatory Note 12). If the spontaneous value is taken as 0.5×10^{-6} this is 20 times the induced rate per rem in the mouse ($.25 \times 10^{-7}$). If the average spontaneous rate is 0.5×10^{-5}, the ratio is 200. So we estimate that the increase in relative mutation risk per rem is between 1/200 and 1/20, or that the doubling dose is between 20 and 200 rem. If we consider the mutation rate for dominant visible mutations—estimated with considerable uncertainty as about 2×10^{-9} per rem—the doubling dose is 100 rem or more unless the spontaneous rate is less than 2×10^{-7}.

The extensive studies in Hiroshima and Nagasaki permit a direct approach to the doubling dose based entirely on human data (see Explanatory Note 6). The death rates in the children of irradiated and control parents did not differ significantly. If the true death rate were one percent higher in the children of irradiated parents, the probability of the observed results in a population as large as this would be less than 0.10. Assume that these parents received a total average dose of 100 rem each. It was estimated that 0.5 percent of liveborn die prior to age 8 as a result of a dominant mutation or chromosome aberration that occurred in the previous generation (41). So we can say that 100 rem, at the most, produced an effect equal to twice the dominant spontaneous rate; the amount required to equal the spontaneous rate for dominant deleterious effects (the "doubling dose") is therefore at least 50 rem. Since this represents acute exposure, whereas we are here concerned with chronic exposure, we estimate that the doubling dose is at least 3 times as large, or at least 150 rem. The 100 rem average dose for the Japanese parents may be too high; if this were only 50 rem then the doubling dose becomes 75 rem. There are many uncertainties in these calculations, but they do offer strong evidence against the doubling dose for mutation being as low as 20 rem of chronic irradiation.

The lowest possible value for the doubling dose is about 3 rem, for this is the amount of radiation received from natural sources in 30 years. Such a doubling dose would imply that *all* spontaneous mutations are caused by natural radiation. Although this possibility cannot be completely ruled out, the evidence is strongly against it. In addition to the estimates given above, there is abundant evidence in experimental organisms for causes of mutation other than radiation. It seems unlikely in the extreme that man differs from all other species in being insensitive to all other causes of spontaneous mutation.

We shall then use a range of 20 to 200 rem for the doubling dose. For reasons given, we doubt that it is below 20 except possibly for some special categories that do not make a large contribution to the total effect. If the true value is greater than 200, then any harm would arise only from being too cautious. As mentioned earlier, the original BEAR Committee used 5 to 150 for its limits; our suggested limits are somewhat higher, reflecting the new information mentioned before.

Calculations based on these assumptions are given in Table 2, which gives the estimated increase to be expected among one million liveborn individuals whose ancestors had received 0.17 mrem per year (or 5 rem per 30-year reproductive generation). If this amount of exposure is continued until an equilibrium is reached, the number of individuals affected with autosomal dominant traits is expected to increase to 10,250-12,500 per million live births, in contrast to the estimated present incidence of 10,000. The calculations are explained in Note 13. The incidence figures are based mainly on an extensive survey in Northern Ireland (3). We have accepted the judgment of the United Nations Report in determining which traits to include. For autosomal dominant traits, there is good reason to think that the equilibrium frequency is proportional to the mutation rate. The assumption is almost as good for X-chromosome-linked recessive traits. The population incidence in Ireland was only 4/5 the incidence among newborn. Therefore, we have assumed that expression in the first generation after radiation is one-fifth the equilibrium value; this is roughly equivalent to assuming that the average mutant persists in the population for 5 generations. The contribution of recessive genes, we believe, is negligible in comparison. For one thing, known recessive diseases are somewhat less common than the dominant. But much more important, the incidence of recessive genes depends strongly on the way selection acts on the heterozygous carriers. A small difference in this can outweigh a large mutational difference. This is especially true if the mutant is favored in the heterozygous state. The incidence is not likely to increase in proportion to the mutation rate. Finally, whatever the equilibrium is, it is attained very slowly, so any effect of an increased mutation rate on the incidence recessive traits would be spread over hundreds of generations.

We can get some support for the numerical values in Table 2 by a different calculation. This again uses mouse data for the induced rate, since there are no suitable human data. But the rest of the calculation involves no assumption about either the doubling dose or the normal incidence. McKusick's tabulation of known Mendelian traits in man lists 415 with dominant inheritance well established and 528 more where the evidence is less complete, a total of very roughly 1000. Assuming the mutation rate in the mouse (0.25×10^{-7} per rem) and 1000 mutable loci (10^3), we compute for one million births (10^6) with a parental exposure of 5 rem a number of new mutants equal to $0.25 \times 10^{-7} \times 10^3 \times 10^6 \times 5 \times 2$, or 250. The final factor of 2 comes from the fact that both parents are irradiated. This value is in the range of first generation values in Table 2 for autosomal dominants. It should be emphasized that this includes only known conditions, not those to be discovered in the future.

The mouse mutation rates that serve as the basis for these estimates are all for recessive mutations. The rates for dominant mutations are known much less reliably, but the evidence is that they may be an order of magnitude lower (4). If this is correct, the values in Table 2 are all 10 times as high as they should be. We prefer, however, to err on the safe side, so we have used the recessive rates.

In addition to the mutation traits summarized in Table 2, there is another class of genetic change—that is, the damage caused by chromosome aberrations, both structural and numerical. There has been great progress in this area recently.

Estimates of cytogenetic effects are given in Table 3. The background for the calculations is given in Explanatory Notes 14 and 15.

The current incidence data are based on surveys of newborn children and on studies of aborted fetuses. The estimated effects from radiation are based solely on information derived from mice. We have assumed, as with other genetic effects, that at low doses the effect is proportional to the dose.

The major contribution to postnatal anomalies is aneuploidy, of which the best known example is mongolism. Since reproduction in this group is virtually zero, the entire incidence must be caused by new occurrences of the chromosome error. The evidence is that this kind of event is not very sensitive to radiation. Some *Drosophila* data suggest a threshold, but there is good evidence that at least some of the effect has linear relationship to dose (See Explanatory Note 16). There have been reports that irradiation of women before conception causes aneuploidy (mongolism), but other and larger studies have failed to confirm this (See Explanatory Note 17). The human data provide no suitable basis for a quantitative assessment and the *Drosophila* data are based on high doses and there is room for considerable doubt about its human relevance. We, therefore, use

Table 2. Estimated effects of radiation for specific genetic damage. The range of estimates is based on doubling doses of 20 and 200 rem. The values given are the expected numbers per million live births.

	Current incidence per million live births	Number that are new mutants	Effect of 5 rem per generation	
			First generation	Equilibrium
Autosomal dominant traits	10,000	2,000	50-500	250-2,500
X-chromosome-linked traits	400	65	0-15	10-100
Recessive traits	1,500	?	very few	very slow increase

Table 3. Estimates of cytogenetic effects from 5 rem per generation. Values are based on a population of one million live births. Unbalanced rearrangements are based on male radiation only.

	Current incidence	Effect of 5 rem per generation	
		First generation	Equilibrium
Congenital anomalies			
Unbalanced rearrangements	1,000	60	75
Aneuploidy	4,000	5*	5
Recognized abortions			
Aneuploidy and polyploidy	35,000	55	55
XO	9,000	15	15
Unbalanced rearrangements	11,000	360	450

*See footnote 1.

mouse data as the basis for the estimated aneuploidy and translocation induction.[1]

It is probable, as Table 3 indicates, that radiation could make some contribution to spontaneous abortions. Although this is certainly not negligible as a source of human distress, it is of much less concern than congenital anomalies of the live-born. There is probably a much larger class of genetic damage that results in failure of the egg to implant or in post-implantation death—that is, too early to be detected. Since this does not have an appreciable effect on human well-being, these mutations have not been included in the calculations.

C. Risk Relative to the Current Incidence of Serious Disabilities

Using 0.005 to 0.05 as the range of values for the relative mutation risk for one rem (or a doubling dose of 20-200 rem) the continuous exposure of 5 rem per 30 years (or about 170 mrem per year) would eventually cause an increase of from 2.5 to 25 percent in the burden of mutation-caused disease.

An unknown, but probably large fraction of human disease is genetically related—at least in the sense that susceptibility depends partly on genetic factors. A detailed survey in Northern Ireland (3) led to the estimate that just over 25 percent of hospital beds and 6 to 8 percent of physicians' time are used by persons with hereditary disease. But we cannot conclude from this that the incidence of such diseases will rise in direct proportion to the mutation rate. The relation between mutation rate and the incidence of complexly-inherited disease is hardly known at all and we shall have to make arbitrary assumptions. Our disease classification follows that of the United Nations Committee.

About one percent of children born have a disease for which there is evidence of dominant or X-linked inheritance, as we have indicated before. Undoubtedly, some of these are inherited in a more complex way, but these are probably balanced by dominant diseases that are not recognized as such. So we shall take one-percent as the figure in this first category. The incidence of these is essentially proportional to the mutation rate.

Recessive diseases, the second category, are less frequent and their incidence is only very indirectly related to the mutation rate. Their total incidence is less than 0.5 percent. Serious diseases caused by chromosome aberrations also have an incidence of about one-half percent, but these are not thought to be greatly increased by low level radiation (See the previous section).

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[1] We are aware that a new study in progress in Hiroshima and Nagasaki is finding increases in sex chromosome trisomy in the progeny of the irradiated population. We are as yet unaware whether this will require revision in our risk estimates, which must await analysis of the data.

Diseases of more complex etiology fall mainly into two groups. One group, our third category, with an overall incidence of abut 2.5 percent of births, consists of malformations. About 1.5 percent are recognizable at birth, the remaining 1 percent developing later. The fourth category contains a mixture of constitutional and degenerative diseases. This figure is taken to be 1.5 percent, but is quite arbitrary, depending on what diseases are included. Anemia, diabetes, schizophrenia and epilepsy, for example, are included. Heart disease, ulcer, and cancer have not been included, although there is known to be a genetic component in each.

We then have a total of about 6 percent of children born who have diseases in these categories. The first category, dominant or X-chromosome-linked diseases, is assumed to increase in proportion to the mutation rate, which means that the eventual incidence will be increased by the dose times the increase in relative risk per rem which we have taken to be between .005 and .05. The first generation effect we again take as 20 percent of this.

The second category, chromosomal and recessive diseases, will have very little increase relative to dominant diseases. The chromosomal effects are not very much increased by low level radiation. Those diseases caused by recessive genes will eventually increase but the amount is uncertain. Furthermore, it would require scores of generations in the future for the full effect to be manifest.

The last two categories present a more difficult problem. The extent to which the incidence of these diseases depends on mutation is not known. We shall define the "mutational component" of a disease as the proportion of its incidence that is directly proportional to the mutation rate. It is not likely to be more than half for diseases considered in these categories. Some would estimate it as low as 5 percent. The values in Table 4 are based on these limits.

To estimate the first generation effects in the last three categories of diseases, we note that the magnitude of the individual gene effects presumably causing these diseases is likely to be less than that of the single gene dominant mutations; therefore, we would expect a smaller fraction of the total impact to be in the first generation. We shall arbitrarily use half the 20 percent value used for dominant diseases, or 10 percent as the fraction of the equilibrium value that is expressed in the first generation, although the true value may well be less.

The Subcommittee is aware that this classification of diseases, based on the U. N. Reports, which in turn were based on surveys in Northern Ireland, is not very detailed and may not be entirely relevant for the United States. It would be possible to get a more detailed specification of the kinds of diseases and their relative incidences. Our reason for not being more specific in this regard is that the other uncertainties are so great. For most diseases, even if we knew the incidence with great accuracy, we could not specify what the mutational component of this is. Until we have quantitative information about radiation-induced mutation *in man* and of the role of mutation in maintaining disease incidence, we think it is pointless to further refine our discussion of specific diseases.

D. The Risk in Terms of Ill Health

There is danger that the previous sections, by concentrating only on fairly well defined genetically-associated diseases, have dealt with only the exposed part of the iceberg. What about the rest of human illness? It, too, has some degree of genetic determination.

The most tangible measure of total genetic damage, in terms that are meaningful and important to human welfare, is probably poor physical and mental health. Although we cannot measure the personal distress that this causes, we can measure morbidity in economic units such as days lost from work or medical expenses.

It seems likely that the mutational component of this unspecified remainder is less than for the categories of Table 4, where the increase that would eventually result from a doubling of the mutation rate was taken to be roughly in the range of 1/4 to 1/2. We assume that the quantitative average is effectively mimicked by a model in which a certain fraction of the incidence has simple linear relationship

Table 4. Estimated effect of 5 rem per generation on a population of one million. This includes conditions for which there is some evidence of a genetic component. This table includes values from tables 2 and 3.

Disease classification	Current incidence	Effect of 5 rem per generation First generation	 Equilibrium
Dominant diseases	10,000	50-500	250-2500
Chromosomal and recessive diseases	10,000	Relatively slight	Very slow increase
Congenital anomalies	15,000	5-500	50-5000
Anomalies expressed later	10,000		
Constitutional and degenerative diseases	15,000		
Total	60,000	60-1000	300-7500

to dose and the rest is not assignable to radiation at all. This fraction was taken as 1/4 to 1/2. For unspecified ill-health, it is probably less, for dominant genes are thought to play a lesser role, and we shall assume a lower value of 1/5. It may well be less, but few would argue that it is much higher, so we take this as a prudent assumption.

Using this value and again taking 20 rem as the lower limit of the mutation rate doubling dose, an exposure of 5 rem per generation would increase the equilibrium ill-health incidence by 5/20 x 1/5 or 5 percent of the present value. With 200 rem as the doubling dose, this would be 0.5 percent.

If desired, this can be converted into economic terms. For one way, see Note 18.

IX. Discussion

A major concern of the Subcommittee is the possible existence of a class of radiation-induced genetic damage that has been left out of the estimates. By relying so heavily on experimental data in the mouse we may have overlooked important effects that are not readily detected in mice, or the mouse may not be a proper laboratory model for the study of man.

Another source of concern is whether the low mutational response to radiation in the female mouse is applicable to the human female. The concern arises over the fact that, for most of their lifetime, the reproductive cells in the female mouse are highly sensitive to cell killing, whereas those in the human are not. This raises the question of whether the low mutational sensitivity of these mouse cells can be assumed to apply to the human cells. However, there is, in general, in the mouse no clear correlation, either negative or positive, between mutational sensitivity and cell killing of the type involved here, in which death occurs before cell division. Furthermore, the germ cells in the female mouse also go through a period when, like the human cells, they are very resistant to killing, and here too the mutational sensitivity, although high with acute irradiation, is very low with chronic irradiation—much lower than that in the male. Thus, although we have some concern about applicability of mouse female data to the human female, there are, so far, no data from any of the various germ cell stages studied in the female mouse that would indicate anything but a very low mutational response, relative to that in the male, under the usual conditions (low dose and low dose rate) of human radiation exposure.

If our estimates of risk are too high, the only dangers are those which might derive from excessive caution, such as regulations which might permit greater hazards from other sources to replace the overestimated radiation hazard thus avoided. A more serious error would be to underestimate the effect. It is impossible to prove absolutely that the doubling dose is not as low as the background radiation level, namely about 3 rem. But all the information from other organisms and the few data that exist for man (mainly from cell cultures and from humans that have been irradiated, especially the Japanese populations) suggest that this value is too low and that our lower limit of 20 rem for chronic radiation is very unlikely to be too high.

We have assumed that data from low doses and low dose-rates in mice are appropriate for the kinds of radiation to which most of the human population will be exposed. The major exceptions are therapeutic radiation, which constitutes very little of the genetically significant dose, and accidents, about which we are in no position to make any specific assumptions.

Perhaps the major reservation that we have about our estimates is their failure to take adequately into account mutations that have very mild effects. As mentioned earlier, this is the most frequent class of mutations in *Drosophila* and because they persist longer in the population than those with more drastic effects, each mutant gene affects a correspondingly larger number of persons. The empirical experiments on mice argue that such genetic mutations are not making any substantial impact on mouse populations for up to 45 generations of continuous radiation—far longer than we are able to consider in any meaningful way for the human population. Yet there is the possibility that one simply does not see in mice effects that would cause appreciable distress in humans.

One way to approach this problem is to use a method that was urged by the late H. J. Muller, who discovered that radiation has genetic effects. As mentioned in the introduction, this was one approach used by the original BEAR Genetics Committee. Since each mutant gene must eventually be eliminated from the population, one can simply measure the total number of mutations produced in a generation; this number is then the number of eventual gene extinctions or "genetic deaths" if the population size remains stable. (If the population grows, the number of gene extinctions increases in proportion.) There is no information given by this calculation about the time distribution of these extinctions. But it must be said that this is one approach that at least attempts to measure the *total* impact of mutation, integrated over all future generations affected by these mutations.

Despite the relative simplicity of this calculation, we have not recommended it as a basis for estimation of the genetic risk. The main reason is the impossibility of equating statistical gene extinctions to any meaningful measure of human misery. A "genetic death" may be the death of an embryo so early that no one ever knows about it, or it may simply be the failure to reproduce. On the other hand, it may be a lingering, painful death in early adult life that causes great distress to the person and his entire family. Also it is not known that mutant genes are always eliminated independently, which the calculation assumes. Furthermore, the calculation depends on the gene number, which for man can only be guessed. Finally, to equate genetic deaths to actual human death, as some have done, gives a quite erroneous picture of the impact of mutation on the population.

We remind all who may use our estimates as a basis for policy decisions that these estimates are an attempt to take into account only known tangible effects of radiation, and that there may well be intangible effects in addition whose cumulative impact may be appreciable, although not novel.

X. Summary and Conclusions

We have reviewed the recommendations and risk estimates of the 1956 National Academy of Sciences Committee on the Biological Effects of Atomic Radiation (BEAR) and believe that, if anything, the risks estimated at that time were on the high side. The main reasons for this are the discoveries that radiation at low dose-rates is considerably less effective than the same dose at a faster rate and that the female mouse is for much of her lifetime very resistant to radiation-induced mutation. Another reason is the failure of mice whose ancestors have been irradiated heavily for many generations (45 in one case) to show measurable effects on viability or fertility.

We recommend that calculations for low doses be made by assuming that the relationship between the lowest accurate measurements and zero induced effect at zero dose is linear. The assumption is plausible for mutations and chromosome breaks; for other effects, such as non-disjunction, which may depend mainly on other mechanisms, it is a conservative procedure in which any error is likely to be on the safe side. We also recommend that, when estimates are made from experimental animals, these be based on chronic or fractionated doses as being more relevant than large, acute doses to the typical conditions of radiation exposure to the human population.

We take the risk of chronic radiation at low doses, relative to the spontaneous mutation rate, to be 0.005 to 0.05 per rem. This relative risk is equivalent to saying that the amount of radiation required to produce as many mutations as occur spontaneously in a single generation (the doubling dose) is between 20 and 200 rem. The information on the radiation-induced effect comes almost entirely from mouse data.

The Subcommittee recommends four bases for assessment of the genetic risk. They are arranged in order of the confidence that we have in them. The first is very firm, the second less so, the third still less, and the fourth little more than an informed guess.

(1) *The risk relative to the natural background radiation.* If the genetically significant exposure is kept well below this amount, we are assured that the additional consequences will be less in quantity and no different in kind from what we have experienced throughout human history. This base, although not quantitative, has the great merit that it is not necessary to make any quantitative assumptions about human radiation genetics.

(2) *The risk of specific genetic conditions.* Using the relative risk (or doubling dose) given above, an estimate of the increase in diseases caused by dominant and X-chromosome-linked recessive mutations can be made for the generation following radiation and for the equilibrium increase under continuous radiation. Estimates of cytogenetic effects can be made directly from mouse data. Numerical values are given in Tables 2 and 3.

(3) *The risk relative to the current incidence of serious disabilities.* Diseases caused by dominant and by X-chromosome-linked recessive mutations will eventually increase in proportion to the mutation rate increase. For congenital anomalies and constitutional diseases, we suggest that the mutational component (or the fraction of the incidence that is proportional to the mutation rate) is between 5 and 50 percent. Numerical values based on these assumptions are given in Table 4.

(4) *The risk in terms of overall ill health.* The contribution of the mutational component to ill health is arbitrarily taken as 20 percent. With this and a doubling dose between 20 and 200 rem a dose of 5 rem per generation would eventually lead to an increase of between 0.5 and 5.0 percent in all illness.

It is clear that these estimates are subject to great uncertainty. The ranges of plausible values are broad, and there is no assurance that the true values are within these ranges. We are well aware that future information will necessitate revisions. The estimates are presented, not as accurate scientific information (as scientists we would prefer to defer judgment until the information is solid), but as reasonable values based on current knowledge which, crude and uncertain as they are, may serve as a better guide to rational uses of radiation than no estimates at all.

In cost-benefit calculations, the discrepancy between cost and benefit may be so great that even such crude and uncertain estimates may be very useful. Whether a risk is acceptable also depends on how avoidable it is. If the genetic risk is easily reduced, it is unacceptable even if the cost-benefit ratio is low.

It seems clear that the genetically significant radiation exposure from fallout, from nuclear power developments, and from occupational exposure (treated as a part of the over-all population average) is now very small relative to that from natural radiation. There is no reason to think that the dose commitment for the development of nuclear power in the next few decades should be more than about a millirem annually. The 1956 report and the guides that grew out of it were the result of an effort to balance genetic risks against the needs of society. It now appears that these needs can be met with very much less than the 170 mrem per year of the current Radiation Protection Guides. Accordingly, the 170 mrem seems to provide an unnecessarily large cushion.

Likewise, we believe that the currently much higher level of radiation from medical sources (mainly diagnostic) should be examined in view of the same concept. If it can be reduced further without impairing essential medical services, then the present level is unnecessarily high.

APPENDICES TO CHAPTER V

Explanatory Notes

Note 1. UNSCEAR Reports

The United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) has issued a series of reports which collectively constitute a wealth of information on this subject (*5-8*).

In general, throughout this report, we shall not further document conclusions that are in the UNSCEAR reports, but instead will simply refer to these reports. The bibliographies therein are very extensive and the reader is referred to them for more detailed information.

We should like to take this opportunity to thank the United Nations Secretariat for supplying us with written material and for individual consultation.

Note 2. History of Radiation Standards

The British report specifically stated: "Those responsible for authorizing the development and use of sources of ionizing radiation should be advised that the upper limit, which future knowledge may set to the total dose of extra radiation which may be received by the population as a whole, is not likely to be more than twice the dose which is already received from the natural background; the recommended figure may indeed be appreciably less than this" (*9*).

In January 1957, the NCRP recommended that the population dose "shall not exceed 14 million man-rems per million of population over the period from conception up to age 30 and one-third that amount in each decade thereafter." This was based on the exposure practices and data of that period and the contributions of the individual sources were estimated in man-rems per million population per 30 years as:

Natural radiation	4,000,000
Medical irradiation	5,000,000
Occupational exposure	150,000
Radiation in plant environs	450,000
Fallout	200,000
Total	9,800,000
Balance	4,200,000

The radiation exposures included medical, natural, and fallout radiation and all other man-made sources and allowed a cushion of over 4 million man-rems for future needs.

In April 1958, the concept of population dose for man-made radiation, exclusive of medical exposure, was made more specific in the statement: "The radiation. . .shall be such that it is improbable that any individual will receive a dose of more than 0.5 rem in any 1 year from external radiation." It was also recommended, as in 1957, that the average body burden of radionuclides not exceed 1/10 that for radiation workers.

In September 1958, the International Commission on Radiological Protection (ICRP) suggested that "the genetic dose to the whole population from all sources, additional to the natural background, should not exceed 5 rems plus the lowest practicable contribution from medical exposure." Because the genetic dose is calculated for a 30-year period, this would amount to an average of 170 mrem per year.

The same value of 170 mrem per year had been arrived at by a different route based on the 0.5 rems per year recommended by the NCRP for an individual in the general population. It was reasoned that to hold the dose to the individual to that level, the average level for a population group would have to be approximately 1/3 of the maximum amount, or again 170 mrem per year. Based on the published recommendations of the NCRP and ICRP, the population average of 170 mrem was adopted by the Federal Radiation Council in 1960.

The history of radiation protection standards has recently been reviewed (*10*). Other references are by NCRP (*11, 12*), the FRC (*13*), and NCRP (*14*).

Note 3. The Number of Genes

Actually, this calculation does not assume that the number of genes is known, but rather it depends on the ratio of the overall mutation rate to that for a single locus. The ratio of the total lethal rate to that for a single locus was multiplied by 2 to 3 to allow for mutations with less than lethal effects. This led to an estimated ratio of about 10^4, subject to considerable uncertainty both as to accuracy of measurement and reliability of assumptions. The conclusion was reinforced by the fact that the number of bands in the salivary gland chromosomes in *Drosophila* is about 5000. There is recent evidence (*15-21*) that the number of genes (complementation units) in *Drosophila* is indeed equal to the number of salivary chromosome bands, which would be 5000 per gamete, or 10,000 in the diploid cell. The human number is probably larger, but there is no comparably reliable way to estimate it. We shall not use the gene number in any of our risk estimates.

Note 4. Effect of Cell Type, Sex, and Rate of Delivery of Radiation

There is evidence from many organisms and many systems. This is reviewed in detail and presented in summarizing tables in UNSCEAR papers. We shall present only a short summary and refer the reader to the UNSCEAR reports for details and references to the original literature.

Some of the best documentation comes from mouse studies and, because it is likely to be more relevant for human risk estimation than data from insects, plants, or cell cultures, we shall present only mouse data here. The following summary, provided by W. L Russell, illustrates the range of sensitivity of different stages in the two sexes. The data are all for single locus recessive mutations induced by acute X-radiation.

Spermatogonia	1.7×10^{-7}/locus/rem
Spermatogonia of newborn	1.3
Mature oocytes	1.8-5.4
Immature oocytes in adults	0
Immature oocytes in newborn	1.0

Data are not given for spermatozoa and spermatids. Although the rates for these cells are considerably higher than for spermatogonia, we have not given them because these stages occupy such a short part of the total pre-reproductive period in man. Likewise, the immature oocyte stage in female mice where mutation production is very low (not significantly different from the spontaneous controls) is a stage of long duration relative to the much more sensitive mature oocytes, or immature oocytes in newborn. In the female, we are less confident of the comparability of mouse and human because of unexplained differences in the cell-kiliing rate (*22,23*).

The dose-rate dependence can also be illustrated from mouse data. For spermatogonia, the rate of production of mutations is about 1/3 as great with low dose-rates of X-rays as with a high dose-rate. There seems to be a comparable reduction when the total dose is small, even if given at a rapid rate. For mature oocytes in the female, the rate of mutation production when the dose is administered at a very slow rate is only about 1/20 the value for the same dose given quickly (*24-29*).

Note 5. Empirical Studies of Mouse Populations

There are several recent reviews of this subject (*30-36*).

Although the simplest approach to assessing radiation risks would seem to be direct observation of harmful changes in offspring and later descendants of irradiated mammals, such studies are generally believed to reveal only part of the total genetic damage. Recessive lethal changes in particular tend to escape detection unless special stocks and special breeding systems are employed, and the same may be said of recessive detrimental changes and mutations associated with small dominant effects. Nevertheless, induced hereditary changes leading to skeletal anomalies (*37*), loss of learning ability, and changes in such quantitative characteristics as body weight (*38, 39*), have been detected by this method.

Where the irradiations have been repeated over many generations, such mammalian studies have posed a curious problem. If, as is generally believed, most induced mutations have slight deleterious effects in the heterozygous state, the continued accumulation of such change without apparent eliminations through deaths and failures to reproduce would be expected to cause eventually some obvious and substantial effects on the members of the population. This has not yet happened in any of the large-scale studies.

Results obtained by Spalding and his coworkers are of special relevance in that the exposures, in this case 200 rems per generation to the male line, were continued over a total of 45 generations. It was reasoned that, if mutations with individually small effects do, in fact, occur with much greater frequency than mutations with major effects, and can accumulate to constitute a damaging genetic load, the presumed effects would eventually be reflected in measurable alterations of the growth and death rates. The experiment was carried out with a highly inbred strain of mice to minimize initial chance differences in the irradiated and unirradiated lines. There were no significant differences between the irradiated and control strains in growth rate or in mortality; the lifetime survival curves are almost identical in the two groups. Other such studies of mammals have shown changes in growth rates, but not in any consistent direction.

As summarized by Green (30), these negative results may be due "to the non-existence of induced mutations having only moderate individual effects on heterozygotes, to the failure to find the right indicator trait, or to the relatively small sizes of the experiments so far conducted and their relative lack of power for discriminating small genetic differences in the presence of large amounts of non-genetic variability."

Note 6. Hiroshima-Nagasaki Studies and Sex-ratio as a Measure of Genetic Effect

The studies of children whose parents were irradiated in the Japanese bombings have been reviewed several times (*40-42*). None of the measures of health and survival showed significant differences, nor did physical measurements.

Special attention has been given to the sex-ratio (*43*). Animal experiments have shown sex-ratio shifts in the direction expected if recessive X-chromosome-linked deleterious or lethal mutations were being produced (*44*). The only results relative to sex-ratio in the Japanese studies that approached statistical significance are changes in the sex-ratio, where the early results are barely significant in the expected direction; but later studies have not confirmed this. There are in the literature eight other studies (*43*), mostly showing results in the expected direction; that is, a reduced proportion of males when the mother is irradiated. Reports that irradiation of females prenatally affects the sex-ratio of their children (*45*) are not confirmed in the much larger and statistically better controlled Japanese study (*46*). However, the sex-ratio although easily obtained from data extensive enough for considerable statistical precision, is notoriously subject to fluctuations for genetically irrelevant reasons in both human and experimental animal populations and the Subcommittee does not believe that sex-ratio is a suitable measure for assessment of the human risk. It is perhaps worth noting that, if the human female is like the mouse in being very resistant to radiation effects, the sex-ratio in the grandchildren of irradiated males may be a more revealing measure of recessive X-chromosomal effects than in the children of irradiated mothers.

There is another reason to be suspicious of sex-ratio data as an indicator of genetic damage. In the female, one of the two X-chromosomes is inactivated in each cell. This could mean that a lethal mutation which, if it were on an autosome would not be expressed because of recessivity, might be expressed if it were on the X-chromosome since it would exert its effect in half the cells. Hence, for this reason as well as the one given in the paragraph above, the absence of a sex-ratio change in the children of irradiated parents may not mean anything.

Much more important, we think, is the absence of significant effects on physical measurements or on health and survival.

Note 7. Effects of Transmutation

Of the radioactive isotopes absorbed by the body, only three (H^3, C^{14}, and P^{32}) are incorporated into DNA where transmutation effects could possibly induce mutations in addition to those induced by the emitted radiation. H^3 becomes helium, C^{14} becomes nitrogen, and P^{32} becomes sulphur.

Committee 24 - Radioactive Nucleic Acids and Precursors - of the National Council on Radiation Protection and Measurements has considered the relative effects of transmutation and radiation from tritium and carbon^{14} and concluded that the effect of radiation greatly outweighs that of transmutation. Transmutation of tritium in DNA thymidine produces mainly single strand breaks. Under normal growth conditions, these breaks are repaired with great efficiency. It has been found that tritium decaying in the five position in the pyrimidine ring in DNA leads to an increased yield of mutations in both microorganisms (*47*) and *Drosophila* (*48*) indicating that transmutations can, indeed, produce mutations. Nonetheless, tritium substitution for hydrogen at this position of the pyrimidine ring is extremely rare since the position binds only about 0.04% of the total nuclear hydrogen. All the experimental evidence overwhelmingly indicates that the effects of intranuclear tritium are produced by beta radiation.

Carbon^{14} can also cause effects from chemical transmutation to nitrogen and these effects should be added to the radiation effects from the beta particle. Nonetheless, when there are many carbon -14 decays per nucleus the radiation effects would again far outweigh the consequences of transmutation. This situation is deemed to be similar to that which occurs with tritium.

Although the transmutation of P^{32} incorporated into DNA can lead to strand breakage and, thus, possibly to mutations, P^{32} is not preferentially located in DNA which makes the transmutation effect less important. Some experimental results with *Drosophila* (*49*) indicate that here there might be a slight effect of transmutation in the induction of mutations. This effect was found to be far less efficient than the irradiation. Under certain conditions (*50*), the transmutation effect was not even noticed. Thus, experimental results in *Drosophila* support the view that the contribution from transmutation is small compared to direct radiation effects.

The general conclusion is that for these nuclides that are incorporated into nucleic acids the beta radiations far outweigh any contribution from transmutation effects and that it is, therefore, justified to consider the main effect to come from the radiation emitted when the isotope disintegrates. This is also true *a fortiori* for those isotopes not incorporated into nucleic acids.

Note 8. The High Frequency and Heterozygous Expression of Minor Mutations

It has been known for many years that minor deleterious mutations in *Drosophila* are more numerous than those that produce a lethal or near-lethal effect. The first accurate quantitative assessment of the mutation rate of such minor genes was by Mukai (*51*), who used the device of letting mutations accumulate on a chromosome that was protected from the effect of natural selection by being kept heterozygous generation after generation with careful precautions to minimize natural selection. From the mean and variance of the decline in viability when such chromosomes were later made homozygous, he inferred that the mutation rate is at least 15 times the lethal mutation rate. These results have recently been confirmed in three independent experiments (*52*). Further confirming evidence comes from microorganisms showing that mutations resulting from substituting one amino acid for another (missense mutations) are very much underrepresented relative to chain-terminating (nonsense) mutations among conditional lethals (*53, 54*). Presumably, the former are producing effects too small to be detected by the system employed.

Although these mutants are found in very high frequency in natural populations of *Drosophila*, they are not as frequent as they would be if they were completely recessive. This means that they must be eliminated from the population through heterozygous effects (55, 52). The high frequency of these mutants and their degree of heterozygous expression is such that they should have appreciable effects on the viability or fertility of the population. An increased mutation rate would, therefore, be expected to cause a general, non-specific reduction in the fitness of the individuals in the population through the production of such mutants.

A mitigating factor is that these individually minor mutants are less frequent, relative to severe mutants, among radiation-induced than among spontaneous mutations (56). Radiation is known to produce genetic changes at all levels—single base replacements, insertions and deletions of nucleotides, changes involving several bases, and on up to gross chromosome rearrangements (57). However, the ratio of deletions and chromosome rearrangements to single base effects is likely to be much higher for radiation-induced than for spontaneous changes.

Note 9. The Kinetics of Mutation and Chromosome Breakage by Radiation

The genetic material is DNA which contains information in the sequence of its four nucleotides. Each sequence of 3 nucleotides (triplet) codes for an amino acid in a protein. A gene is composed of many hundreds or more of nucleotides in a specific sequence. Not all DNA codes for proteins; probably the great majority has other functions, largely unknown. The DNA itself is organized into larger linear nucleoprotein structures, the chromosomes, found in the nucleus of the cell.

Any change of a nucleotide such that a given triplet will now code for a different amino acid constitutes a mutation. Other changes in coding also can have mutagenic consequences. For instance, the addition, or deletion, of a nucleotide from DNA will shift the reading sequence of the code, since it is read 3 nucleotides at a time sequentially. Such frame shift mutants will change whole sequences of amino acids in the protein up to the point where a reverse shift can put the reading back into proper register. Thus, even a change, deletion, or addition of a single nucleotide in DNA can be a mutation.

In addition, a larger class of mutational events arises from the breakage of the chromosome itself with subsequent deletion or rearrangement of the broken pieces. These changes are often large enough to be seen if the chromosomes are examined under the microscope. Their size distribution, however, forms a continuum from the very small deletion of a single nucleotide to the loss of a whole chromosome. At the bottom of the range, it is impossible to define just where a deletion should be considered a point mutation in the gene rather than a chromosome breakage type of mutation. For most of the chromosome rearrangements considered in this context, with low LET irradiation, the frequency of induced rearrangements is proportional to the dose over the dose range of interest. At higher doses, more complex kinetics are observed (58).

Note 10. The Linearity, No-threshold Assumption

As outlined in the Note 9, there is strong evidence that, for single locus mutations in *Drosophila*, the dose-response relationship is linear down to the lowest doses that have been adequately tested. There is no evidence for any threshold. If there is none, then the curve, when extrapolated to lower doses, should intersect the zero-dose ordinate at a value equal to the spontaneous rate. The observations are compatible with this, but the statistical error is too large for this expectation to be tested with any rigor.

As mentioned in the previous note, another reason to expect a linear relationship is that for very low doses there is very little opportunity for ionizations from independent ion tracks to occur in the same cell locality. Any effect following exponential kinetics with an exponent larger than one is bound to disappear at sufficiently low doses.

For phenomena involving breaking and rejoining chromosomes, such as reciprocal translocations, it is usual (as stated in the previous note) to have a power curve at moderate doses. However, the data for translocation production in *Drosophila* oocytes are best fitted by a curve with both a linear and a quadratic component. At low doses, the quadratic component becomes negligible. This is readily understood; even if the translocation requires two or more ionizations, these are much more likely to be part of the same ion-cluster than from independent ion tracks. So we expect the linear component to predominate greatly at doses that commonly apply to the human population.

In the mouse, two opposite types of departure from linearity have been found for acute irradiation of spermatogonia. One of these has been explained by differential cell killing, and the other by repair of premutational damage.

The first departure consists of an upward convexity of the dose-effect curve at high doses: an x-ray dose of 1000 R actually produced fewer mutations than did a dose of 600 R (*59, 60*). Russell's hypothesis to account for this result is that in the heterogeneous population of spermatogonial cells some cells are more sensitive to both killing and mutation. Thus, at high doses, the sensitive cells are destroyed, leaving only those cell types that produce fewer mutations. If this effect were to extend down to lower dose levels, then the mutation rate at these levels would be higher than predicted from a linear interpolation between 600 R and 0 R. However, at 300 R, no significant departure from linearity was observed. Recent work by Oakberg (*61*) indicates that the true stem cells in the mouse testis are not as easily killed by radiation as are the rest of the spermatogonia, and that differential killing among these stem cells is not, in fact, likely to have any humping effect on the dose curve in the range below 500 R. Furthermore, mutation-rate studies in the low dose range indicate that if there is any tendency toward such a humping it is more than counterbalanced by the opposite departure from linearity, to be described below.

In *Drosophila*, on the other hand, Oftedal (*62*) has reported that spermatogonial mutations produced in the 0-300 R interval indicate a relatively higher mutagenicity of the lower doses in the range. He accounted for this in terms of the hypothesis invoked by Russell to explain the similar effect found in the 600-1000 R interval for the mouse. There are doubts about the statistical significance of Oftedal's results, and large-scale studies done by Abrahamson (*63*) in an attempt to check them have failed to reveal any evidence for a significantly increased mutation rate per R at doses of 20 and 100 R relative to 500 R. Abrahamson's results at face value point in the opposite direction, but are not significantly different from linearity.

The second type of departure from linearity observed in the mouse consists of an upward concavity of the dose-effect curve at low doses (*26*). This non-linear relation for mutations that seem to be mainly the result of single-track ionization events (*26, 64-66*) is explained on the hypothesis that there is repair of mutational or premutational damage, but that the repair process is either damaged or saturated at high doses and high dose rates. This hypothesis, which was originally derived from the discovery of a dose-rate effect in mouse spermatogonia and oocytes (*67, 68*), predicts that repair could operate even at high dose rates, provided that the total dose were small or given in small fractions at intervals long enough for the repair process to recover. As shown above, this prediction was met for small total doses. It has also proved true for fractionation.

The finding of a dose-rate effect for mutation induction in mouse spermatogonia and oocytes raised anew the question of whether there might be a threshold dose or dose rate below which all mutational damage would be repaired. Exploration of a range of dose rates provides no evidence of a threshold dose rate for mutation induction in mouse spermatogonia (*26, 69, 70*). Mutation frequency drops as the dose rate is lowered from 90 R/min through 9 R/min to 0.8 R/min; but below that level, to 0.009 R/min and even 0.001 R/min, there is no further reduction in mutation frequency. Therefore, we shall make the prudent assumptions that there is no threshold dose rate in the male and that the dose response at low dose rates is linear.

The female mouse, in contrast to the male, shows no levelling-off or plateau in mutation frequencies as the dose rate is lowered (*26, 69, 70*). At the lowest dose rate tested, 0.009 R/min, the mutation frequencies, even from high doses, are not significantly higher than in controls.

Note 11. The Reason for Using Chronic Radiation to the Mouse Male as the Basis of Calculations

Mature oocytes in the mouse are relatively susceptible to radiation effects. The rate of production of point mutations is about 5×10^{-7} per locus per rem with acute radiation. However, there is a reduction to about 1/20 of this amount for chronic radiation. The stages prior to the mature oocyte are very resistant to mutation; hardly any mutations are produced. In the mouse the duration of the mature oocyte is about 7 weeks. It is reasonable to assume that in humans the stage of sensitivity is short relative to the total pre-reproductive life cycle, as it is in the mouse, but there is no direct evidence for this.

Likewise, mature spermatozoa and spermatids are more susceptible to radiation-induced mutation than spermatogonia, and there is no reduction in susceptibility with low dose-rate. Again, however, the time that a particular cohort of germ cells is in the mature sperm stage is a small fraction of the whole period between conception and reproduction (See Note 4).

Human exposure to radiation, insofar as this is genetically significant, is almost always in very low doses. Of the total contribution from medical radiation by far the greatest contribution is from diagnostic rather than therapeutic radiation. Therapeutic radiation involves large doses at high rates, but most persons receiving such radiation are past the age of reproduction, or for other reasons are not likely to reproduce, or the irradiated region does not include the gonads. Diagnostic radiation is in small doses, although the rate may be fairly high. However, the total dosage is usually so small as to be more comparable to the chronic or fractionated-dosage mouse experiments. Radiation from sources related to nuclear energy is small in amount and given at a slow rate. For these reasons, the mouse data on chronic irradiation and fractionated doses are more relevant for estimation of the human risk than experiments with high doses and high dose-rates.

Note 12. The Average Human Mutation Rate

A recent discussion of human mutation rates and of the reasons for thinking that most measured rates are higher than the true average is given by Cavalli and Bodmer (*71*). Mutation rates in the literature, which average around 2×10^{-5} are clearly a selected sample. When a study was made of all X-linked mutants found in a complete population survey, the mean mutation rate for mutants found in the survey was about 0.4×10^{-5}. However, there is reason to think that the true average may be still less because traits which are recognized as being caused by mutant genes are more likely to be recognized if the mutant has been studied before; hence, there may still be a bias in favor of those with higher rates. Cavalli and Bodmer suggest that this may lower the average by another factor of 10. We shall assume that the true average lies between these values and, therefore, we take 0.5×10^{-5} and 0.5×10^{-6} as reasonable limits for the average mutation rate for human recessive genes.

Note 13. The Calculations for Table 2

If the doubling dose is 200 rem, then 5 rem per generation will lead to an equilibrium increase of 5/200. For autosomal dominant traits, the present incidence is 10,000 per million; 5/200 x 10,000 = 250, the lower limit for the equilibrium value in Table 1. If the doubling dose is 20 rem, or 1/10 as much, then the equilibrium value will be 10 times as high, or 2,500. Of this amount, 20 percent is expected in the first generation, and the value would slowly rise to the equilibrium numbers if the radiation were continued at this rate generation after generation.

Similar considerations apply to the X-linked calculations. The recessive X-linked genes listed in the 1958 United Nations report (*5*), as well as the autosomal recessive genes, caused a greater reduction in viability than the dominants. The data suggest that the average fitness is roughly one-half normal. At equilibrium, the incidence of affected individuals, which will nearly all be males, is approximately three times the mutation rate. (The equilibrium gene frequency is 3u/s, where u is the mutation rate and s in this case is 1/2. So the proportion affected among males is 6u, or among both sexes, since only males are significantly affected, is 3u.) The incidence of persons affected by a new mutation is one-half the mutation rate (in this case, the mutation rate in females, since the affected males get their mutant gene from their mother). So we would expect the number of persons affected by new mutants to be about 1/6 of the equilibrium number, less than this if the female mutation rate in humans is less than the male, as it is in mice. One-sixth of 400 is about 65, so the number of new mutants is estimated to be not greater than this. For a 20 rem doubling dose, the equilibrium value for 5 rem each generation will be (5/20) x 400 or 100. This is the upper limit estimate; the lower limit may be close to zero if the female is relatively insensitive to radiation effects.

Note 14. Chromosome Rearrangements in the Mouse

Translocations can be detected in the mouse by the semisterility of heterozygotes or by the cytological observation of special preparations of spermatocytes, looking for multivalents at diakinesis or metaphase (*72*). In the latter method, spermatocytes of irradiated males are examined after appropriate delays to detect translocations induced earlier in spermatogonia. This method is very much more efficient in scoring than are genetic tests based on partial sterility, and produces a translocation count following spermatogonial irradiation about twice that obtained by the semisterility method (*73*). No assumption other than selective elimination of some translocation-bearing cells can account for the discrepancy in the two methods of screening. We shall use semisterility data in the mouse as the basis for our calculations, since this method provides a more accurate measure of the number of viable zygotes produced. Recent data, corrected for the control rate of semisterility, give 3.4 x 10^{-5}/gamete/R as the rate of induction (*74*). There are a number of studies showing essential linearity at lower doses (*63*). Recent work has revealed a dose-rate effect with X-rays as well as gamma radiation, the reduction in incidence of translocations being greater than 2-fold at the lower dose rates (*75, 76*).

The situation in the female is more complicated. Irradiation of the mouse oocyte rather frequently leads to the recovery of semisterile daughters but not of semisterile sons. Apparently not all reciprocal translocations are recovered. We shall use the face value data from semisterility following oocyte radiation, which gives about 3 x 10^{-5}. However, there are no data that we know of for earlier stages. This is a serious gap in knowledge, for we don't know whether this will be like the situation in mutation production, where irradiation of earlier stages has virtually no effect.

Translocations make up the great bulk of the chromosome rearrangements (the reason for this is that there is a much greater chance that the induced breaks will be in different chromosomes than in the same chromosome). Inversions can be screened for anaphase bridges and fragments at anaphase I following earlier radiation, but it is not yet clear how accurate this is as a basis for assessment of the radiation risk. The consequences, however, should either be semisterility or the selective elimination of aneuploid gametes, hence estimates of semisterility in the following note will include risks from inversions.

Note 15. Calculations for Table 3

The numerical values in Table 3 come from a number of sources. The data for current incidence are from population surveys of newborn (for a summary see Ref. 77) and studies of aborted fetuses (*78-80*). The estimates of radiation effects all depend on mouse data.

With chronic radiation the rate of X-chromosome loss when female mice are treated in the oocyte stage is about 6 x 10^{-6} per gamete (*81*). The rate from treated spermatogonia was not significantly different from the control rate. Assuming the same effectiveness for the human, the fraction of XO among all zygotes would be half the above fraction, since half the deficient eggs are fertilized by Y-bearing sperm and die as very early embryos. The effect of 5 rem would then be

$$5 \times 6 \times 10^{-6} \times 1/2 = 15 \times 10^{-6}.$$

This is the source of the number 15 for XO among recognized abortions in Table 3. In humans only about one in 40 of this type survives to birth, so the frequency of induced XO types among live-born infants would be less than one per million. The other monosomic types die so early that they are not detected as abortions and, therefore, make a negligible contribution to human distress.

There are no comparable mouse data for trisomy. The frequency of radiation-induced trisomy for the X-chromosome of *Drosophila* is about 1/4 that of the corresponding monosomy. Taking all this at face value for human chromosomes, the frequency of trisomy for the 22 human autosomes with 5 rem exposure would be

$$5 \times 6 \times 10^{-6} \times 22 \times 1/4 = 165 \times 10^{-6}.$$

Carr (*78*) estimates that about one-third survive long enough to produce recognized abortions, so the frequency of abortions from this cause per million live births is about 55. A small fraction of this number would survive to produce live births with congenital defects. Again, we are taking the mouse data at face value, which yields a negligible effect from irradiated males.

To estimate the number of unbalanced rearrangements induced by 5 rem, we rely on translocations leading to semisterility in the mouse. For low dose irradiation, the frequency of semisterility among progeny of males irradiated in the spermatogonial stages is about 1.5×10^{-5} per rem. There is some indication that the rate in humans may be higher. This comes from studies of Brewen (82) (unpublished) which show in lymphocyte cell cultures twice as many dicentrics in human cells as in mouse cells. There is good reason to believe that at low doses the number of translocations should be approximately equal to the number of dicentrics; for chromatid breaks this has been shown experimentally (83). In the absence of better information, we shall estimate the human rate by doubling that for the mouse.

Only balanced translocations are detected as semisterility in the offspring. The ratio of the frequency of undetected, unbalanced translocations to that of balanced translocations in the offspring of irradiated individuals depends on a number of unknown factors. Under certain and possibly unrealistic assumptions (such as random segregation in a ring quadrivalent) it might be as high as 4:1. On the other hand, in a chain quadrivalent, 2:1 appears more likely. With an excess of alternate segregations, a ratio of 0:1 may be approached. However, all this applies only if the translocation took place between chromosomes. In the case of chromatid translocations, the ratio may be extremely high because the mitotic descendants of the cell in which the breakage occurred are likely to be already unbalanced. Since radiation may induce chromosome breaks as well as chromatid breaks, and we do not know which type is more common in the germ line, we shall use 4:1 as a reasonably conservative overall estimate of the ratio. The estimate for 5 rem to spermatogonia is

$$5 \times 1.5 \times 10^{-5} \times 2 \times 4 = 600 \times 10^{-6}.$$

The estimates for progeny of irradiated females are still more dubious. The amount of semisterility in the progeny of irradiated females is about the same as for males with acute radiation. However, the relative effectiveness of chronic radiation may be less than for spermatogonia. Translocations induced in oocytes are chromatid exchanges; the ratio of balanced to unbalanced gametes is unknown. There are also some unexplained peculiarites in the female mouse data referred to in Note 14. We are aware of no quantitative data on translocation production in female mice from radiation of stages before the mature oocyte. For single locus mutations, these stages are much less sensitive to radiation, indeed almost immune. This may be true for translocations as well, but we are not sure. For all these reasons, we hardly know how to begin a quantitative measure. It is not likely that the female rate is higher than the male, so we shall again be conservative and simply assume the male rate.

Doubling the male rate, we get 1200 unbalanced and 300 balanced translocations in a population of 1 million exposed to 5 rem. Most of these would eventually be eliminated from the population in the form of very early embryonic deaths that are not detected. It has been estimated that about 30 percent would be expressed as recognized abortions. The number leading to congenital anomalies among the liveborn is a much smaller fraction, probably considerably less than 5 percent. Taking 5 percent of 1500 as the upper limit for congenital anomalies and 30 percent as the estimate for abortions gives the values 75 and 450, given as equilibrium values in Table 3. The unbalanced products would affect the first generation, so this is 12/15 of the total.

The values in Table 3 very likely are too high, for the various reasons given above. We are not completely sanguine, however. In mammalian cell cultures, including human, the production of translocations by radiation compared with the spontaneous rate suggests a very low doubling dose. It is not clear what the fate of these would be if they occurred in germ cells. Many may be eliminated through individual cell deaths.

Note 16. Radiation Induced Nondisjunction: Is there a Threshold?

Recent work on the induction of nondisjunction in the fruit fly by ionizing radiations has led to two quite different interpretations. Reports from one laboratory (*84, 85*) suggest that chromosomal interchange may play a significant role in bringing about improper segregations of chromosomes as a result of misalignments on the meiotic spindle at division I. An alternative hypothesis of a threshold dose below which nondisjunction cannot be induced has been proposed (*86*), based on the failure to find increases in sex chromosome trisomy at doses below 1200 R. However, a more recent report from the latter laboratory (*87*), shows that an appreciable fraction of sex chromosome monosomics are also trisomic for the small fourth chromosome, a finding that is required by the interchange model. Since negative findings can scarcely provide evidence of total lack of an effect at low doses, it seems prudent to suppose that nondisjunctions may result from radiation-induced breakage and interchange, or possibly from other events for which thresholds cannot be demonstrated.

Note 17. Is Maternal Radiation a Significant Cause of Human Nondisjunction?

The only human observations that are relevant to this question pertain to autosomal trisomy, especially trisomy 21 which results in mongolism (Down's syndrome). One group of studies, retrospective and prospective, deals with medical radiation, mostly for diagnostic purposes, and shows a significant association between pre-conception radiation of the mother and the probability of the child being trisomic. The association was found in the retrospective studies by Uchida and Curtis (*88*), with 81 mothers of mongoloid children and 81 matched controls, and by Sigler et al. (*89*), with 216 in each group. Another study (*90*), failed to show even a trace of the effect, but since there were only 51 mothers of mongoloid children and 51 matched controls these data hardly carry enough weight to invalidate the other studies, especially since the prospective study by Uchida et al (*91*) again revealed a significant association.

The large body of data from Hiroshima and Nagasaki (*92*) fails to show any relationship between irradiation and mongolism. The discrepancy between the two sets of data is highly significant under any reasonable assumption of the dosages involved in the medical radiation. The fact that the Japanese study involved large numbers of normal people (not patients), was done prospectively, and involved the entire population of newborns, all carefully examined, gives it statistical precision and makes it less susceptible to possible extraneous causes. A possible alternative explanation of the studies involving medical x-rays is that, other factors being equal, women who are receiving x-rays are in poorer health than those who are not and that the poor health is the cause of nondisjunction.

It is likely that high doses of radiation will cause nondisjunction in man just as it does in *Drosophila* and probably does in the mouse. However, the mouse data are concerned with monosomy rather than trisomy and chromosome loss can occur through processes other than nondisjunction. The way that high doses of radiaton upset normal disjunction may be quite different from the way in which other genetic effects are produced. The radiation may act on the spindle and, in particular, may not be produced by a single ion cluster. Therefore, the argument against a threshold used for other genetic effects may not apply to nondisjunction.

In view of the fact (reported in Note 16) that chromosome interchanges, known to be caused by radiation, can cause nondisjunction in *Drosophila*, it would be imprudent to assume an absolute threshold. Hence, our calculations are done on a linear assumption as described in Note 15. This may lead to a gross overestimate of the risk, but it is very unlikely to be an underestimate.

Note 18. An Attempt to Measure the Economic Cost of Radiation

Cost-benefit calculations may necessitate that the cost of radiation exposure be measured in direct economic terms such as dollars. We give here an illustrative example of how this might be done, patterned after Lederberg (*93, 94*).

Assume that the present cost per capita for poor health is $400 per year. (This is based on an estimated $80 billion in medical expenses in 1970 and a population of about 200 million.) $400 per year is $12,000 for a 30-year period. In section VIII-D we estimated that the equilibrium amount of illness from 5 rem of exposure per 30-year generation would be increased between 0.5 and 5 percent. One rem would produce an increase of 0.1 to 1.0 percent. As fractions of $12,000, these percents are $12 and $120. Thus, one rem per generation continued until equilibrium is reached would add an amount of illness equivalent to a cost of $12 to $120 per person per 30 years. This implies that the amount of damage done by one rem, when integrated over all future generations corresponds to a cost of $12-120 - regardless of whether equilibrium has yet been reached or not.

Thus we say: The total future cost of one man-rem, in terms of health costs paid for in present dollars, is between $12 and $120.

This may provide one way for putting a dollar value on a dose commitment of one rem that could be used in cost-benefit calculations. The cost would be distributed over many generations in the future.

We do not undertake to analyze the moral or economic implications of choosing a discount rate for genetic damage that is expressed far in the future, nor do we allow for changes in the purchasing power of a dollar. We do not intend to imply that all money spent for health costs is directly caused by ill-health, nor on the contrary that this represents the total costs of poor health. Furthermore, our presentation of a suggested dollar equivalent for the illness induced by one rem does not imply that we seek to exchange dollars for lives. It is essential, however, that our society elaborate some rationale for the allocation of resources in the interest of maximizing our health - a task that demands further analysis by specialists in health economics.

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CHAPTER VI

EFFECTS OF IONIZING RADIATION ON GROWTH AND DEVELOPMENT

I. Introduction 74
II. Effects of Radiation on Human Development and Growth 74
  A. Intrauterine Irradiation 74
  B. Postnatal Irradiation 76
  C. Acute Effects of Radiation on the Human Fetus 76
III. Biologic Basis of the Special Vulnerability of Developing Organisms 77
IV. Experimental Irradiation of Mammals 78
V. Effects of Radiation on the Development of Behavior and other Functions 78
VI. Effects of Irradiation from Radionuclides 79
VII. Estimates of Risks from Irradiation in Early Life 80
VIII. Summary 80
References 81

CHAPTER VI

EFFECTS OF IONIZING RADIATION ON GROWTH AND DEVELOPMENT

I. Introduction

This chapter reviews briefly the effects other than neoplasia of *in utero* and juvenile exposure to ionizing radiation. Effects on human beings are of major concern, but, since data on human effects are limited, experimental animal data are included. Morphologic changes produced by radiation, effects on behavioral development, and other functional alterations are considered, with particular attention to the special vulnerability of the young and to the lowest exposure levels at which radiation effects can be observed. The references cited treat special points or provide broad coverage and lead to more extensive bibliographies.

II. Effects of radiation on Human Development and Growth

Ionizing radiation has three major effects on human development: impairment of growth, microcephaly, and mental retardation. Knowledge about the dose levels at which these effects occur comes principally from data relating to: 1) patients irradiated for medical reasons, 2) the Hiroshima-Nagasaki survivors of the atomic bombs, and 3) the people of the Marshall Islands who were exposed to nuclear fallout in 1954.

A. Intrauterine Irradiation

Among the earliest reports of the deleterious effects of radiation on human development were Zappert's (65) 1926 account of 21 persons and the 1929 reports by Goldstein and Murphy (22) (see also Van Cleave (*59*) for review) on 75 individuals exposed *in utero* when their mothers were being treated with radiation to the pelvic area. Although it is impossible now to estimate the range of the doses, they were of the magnitude (several hundred rads delivered by x ray or radium) used at that time for treatment of such gynecological conditions as myoma of the uterus, cancer, and abnormal uterine bleeding. Microcephaly, with concomitant mental retardation, as well as eye defects and general impairment of body growth were frequently found among those offspring. In the Goldstein and Murphy series, 38 of the 75 were considered to be in ill health, and of these 18 were microcephalic and severely mentally defective. The authors attributed the condition of two of these children to causes other than radiation. Two other children were mongoloid, but were considered also to have radiogenic microcephaly. The finding of 14 or more mentally retarded microcephalics among 75 individuals exposed *in utero* to therapeutic levels of radiation indicated a strong association between radiation and abnormal development.

Dekaban (*12*), in a retrospective study of 26 cases of *in utero* exposure, attempted to correlate developmental abnormalities with estimated dosage and gestation age at time of exposure. He found that in one case in which the exposure was believed to have occurred between 2 and 4 weeks after conception no abnormality was reported in the offspring. In 22 cases in which the exposure was reported to have occurred from 3 to 20 weeks after conception, either microcephaly or mental retardation, or both, occurred in every case. In three cases, exposed 19 to 25 weeks after conception, no abnormalities were apparent. In the 22 cases of mental retardation and microcephaly, doses varied but were estimated to have been 250 R or more. Again, the cause-effect association is strong, although in such a study, based entirely on published data, such possibly confounding factors as maternal diseases, genetic factors, and environmental influences cannot be ruled out as potential contributors.

From a sample of 1,265 subjects exposed *in utero* at Hiroshima, the cases of 183 who were then available were analyzed by Miller (28) and Wood (*62, 63*) in 1954 and 1967. Of these, 78 were fetuses of less than 16 weeks at the time of irradiation; 105 were 16 weeks or more. Of the 78, 25 showed a significant degree of microcephaly (head circumference more than two standard deviations below the mean for age and sex), and 11 were mentally deficient. Of the 105, 7 were microcephalic as defined and 4 were mentally deficient. The likelihood of microcephaly was proportional to proximity to the hypocenter. In 14 of the offspring with smaller than normal head circumference who were also mentally deficient, 10 were ≥2. S.D. below the mean height for age and sex. In 16 children with small heads who were not mentally deficient, there was no reduction in stature. Table 1 summarizes some of the characteristics of the 78 exposed *in utero* before the 16th week of gestation (*28, 63*).

Other studies of the Japanese, 1613 in all, exposed *in utero* to radiation from the atomic bombs revealed a more general deleterious effect of radiation on body growth (*64, 57*). These subjects were examined annually to assess the effects of the bombs; by age 17, when mature growth had largely been obtained, about 80% were available for examination.

This sample was divided into three main comparison groups: those exposed within 2000 meters of the hypocenter of the bomb; those between 3000 and 5000 meters from the hypocenter; and those entirely outside of the cities. In the group less than 2000 meters from the bomb, the mean head circumference, height, and weight were less than in the two groups exposed at greater distances. In a narrower comparison of subsamples, children exposed within 1500 meters of the hypocenter of the

Table 1
Numbers of children with small head circumference and/or mental retardation following intrauterine exposure to the Hiroshima bomb according to distance from the hypocenter and gestational age category (after Wood et al. (*63*))

Distance from Hypocenter (meters)	Mentally Retarded Head Circumference			Normal Intelligence Head Circumference		Total Examined **
Exposure within 15 weeks of mother's last menstrual period	>3SD*	2 to 3 SD*	<2SD*	>3SD*	2 to 3 SD*	
≤1200	6	2	0	1	0	11
1201-1500	0***	0	0	2	6	23***
1501-1800	0	1	0	0	5	22
1801-2200	0	0	0	0	0	20
Exposure after 15 weeks since mother's last menstrual period						
≤1200	2	0	0	0	0	13
1201-1500	0	0	1	1	1	46
1501-1800	0	0	0	0	2	46

* SD = Standard deviations below the average for age and sex.

** Some children were normal with respect to both intelligence and head circumference; thus the numbers in columns 2-6 do not add to the totals in column 7

*** Excludes 2 with pre-existent Down's syndrome

Hiroshima bomb were, on the average, 2.25 cm. shorter, 3 kg lighter, and 1.1 cm less in head circumference than those in the outer groups. The dose in this zone was estimated in 1957 at 50 rads or more; however, a revision of the dose estimates in 1965, applied to those samples, reduces the dose estimate to about 25 rads (*66*).[1]

Assigning a cause in any case of mental retardation is difficult because few specific causes are known, and when the primary cause is established, secondary contributory factors may worsen or ameliorate the condition. In the Japanese children the diagnosis was applied only if the individual was unable to perform simple calculations, to make simple conversation, to care for himself, or if he were completely unmanageable, or had been institutionalized. The first three of these criteria are usually those which are used to categorize individuals as "profoundly" mentally retarded; the other two criteria are not rigidly defined. This "profound" mental retardation was not observed below 50 rads of maternal exposure (*5, 67*).

Irradiation of the fetus from diagnostic procedures up to a few rads has not been observed to cause developmental abnormalities (*32*), although an excess of malignancy later in childhood has been attributed to the source (*54*). Irradiation of the fetal thyroid by iodine-131 administered therapeutically to the mother might be expected to mimic the effects experienced by Marshall Islanders, (discussed below) but the evidence seems inconclusive (*38, 2*).

B. Postnatal irradiation.

Apart from the Hiroshima-Nagasaki data, and that relating to the effects of nuclear fallout on the Marshall Island of Rongelap, discussed below, most of the data available about the effects of radiation on infants and children is derived from case reports on individuals. Large doses to a part of the body have resulted in impairment of skeletal growth (*11, 49, 58*). As much as 1000 rads (in divided doses) administered therapeutically to the spine in children of various ages had no visible effect, but 2000 rads led to deformity (*31*). Less radiation, 800 rads, to the epiphyses of long bones in infancy permanently stunted growth of the bone.

A recent survey compared children whose scalps were x-irradiated for depilatory purposes in the treatment of fungus infections between 1940 and 1959 with children treated with drugs. Age at irradiation varied from 3 to 12 years and the dose to the scalp ranged from 450 to 850 rads. Subsequent incidence of personality disorders was four and a half times higher in the irradiated group than in the other. For psychoses, the incidence was 2 1/2 times greater and, for psychoneurosis, 3 times greater in the irradiated group (*1, 48*).

Among the Rongelap children exposed to radioactive fallout, two boys who were infants at the time of exposure developed atrophy of the thyroid before puberty. Their whole body dose from externally deposited fallout has been estimated at 175 rads, but owing to concentration of iodine-131 in the thyroid, between 700 and 1400 rads was absorbed by that organ. The atrophy was associated with hypothyroidism, and the resultant retardation of body growth and sluggishness of behavior were attributed to the thyroid deficiency rather than directly to the whole body exposure (*9, 55, 56*).

The most conclusive evidence of postnatal radiation effects comes from a multivariate analysis of anthropometric data on children exposed to the Hiroshima bomb and examined periodically up to eight years later (*30*). As radiation exposure increased, there were, in those receiving doses of 100 rads or more, small but statistically significant decreases in body measurements among children of all ages and in growth rate among adolescents. The extent to which such differences may be due to variables other than radiation exposure—such as socioeconomic inequalities due to blast or fire—is unknown.

C. Acute Effects of Radiation on the Human Fetus

There are almost no published reports of autopsies on individuals exposed to radiation

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[1] These dose estimates, drawn from ABCC data, are of air doses to the mother. The degree of attenuation of the dose in reaching the fetus would depend on such factors as fetal age; e.g., the younger the fetus, the greater the attenuation. An equation to allow for this attenuation in computing fetal dose has not been formulated. (See p. 166, Somatic Report: "Under the conservative assumption that half of the dose was attenuated by the mothers' bodies...")

in utero or in early postnatal life, in respect to either immediate or late effects. Driscoll *et al.* (*14*) were able to study the acute effects in two human fetuses exposed to radiation from the radium with which their mothers were being treated for cancer of the cervix. The fetuses, 15 cm and 21 cm in crown-rump length, were examined 2 and 10 days after the beginning of irradiation, which lasted 48 hours in the first case and 4 days in the second. The crowns of the heads were about 5 cm distant from the source and received about 800 R and 1600 R, respectively. Destruction of primitive proliferative and migratory cells in the brains and of granulopoietic cells in the hematopoietic tissues occured in both, but evidence of acute necrosis of lymphoid and mesenchymal cells was still visible only in the smaller fetus exposed for 48 hours. Mesenchyme cell necrosis extended as far as the kidney, where the dose may have been of the order of 50 to 100 rads in this fetus. In the larger fetus exposed for 4 days, more degenerating ova were seen than in comparable unirradiated subjects. These observations provide a link between human and laboratory animal data, suggesting that patterns of cellular radio-sensitivity in man are similar to those in other mammals.

III. Biologic Basis of the Special Vulnerability of Developing Organisms.

The developing organism is especially vulnerable to radiation damage, not because the primary interactions between radiation and its biological system differ from those in the adult, but because of properties peculiar to that period of life. The embryonic, fetal, and infant mammals are organizations of progressively changing cell populations whose proliferating, interacting, and differentiating members are never long in a steady state. The cells are not only changing at the molecular level, but are often migrating. This changing cellular mosiac responds differently to radiation from moment to moment, and the changes in sensitivity accompanying different stages of development combined with different doses of radiation present a staggering number of possible combinations of effects (*39-42, 52*). Nonetheless, various mammalian species show some fundamental similarities in response when the irradiation[2] occurs at comparable stages of fetal development (*7, 10, 14, 20, 22-24, 39-41, 52, 59*).

Radiation exposure may kill or damage proliferating and primitive cells. While such losses can often be made up by the regulative (regenerative) capacity of the embryo, the death or injury of large numbers of cells engaged in key inductive processes can cause serious failures of development (*23, 36*). Radiation effects in the early mammalian embryos closely mimic the effects caused by surgical extirpation as practiced in classical experimental embryology. Gross anatomic abnormalities of entire organ systems may follow radiation exposure in the early periods of organogenesis.

In addition to its effects directly on the cell, radiation exposure can permanently alter the differentiation of large populations of maturing cells by destroying or altering some of the DNA or other biologically active molecules essential at the moment to ensure the sequence of proteins necessary for the cells' normal growth and development (*13, 45*); somatic mutations, also, may occasionally be established in developing cell lines (*43*). Both mechanisms can initiate modifications in structural and functional development.

Radiation effects may appear almost at once, they may be delayed, or they may set in motion a chain of recognizable secondary events. Thus, the destruction of primitive and proliferative cells in many organs and tissues in embryos during organogenesis may begin to appear within an hour after irradiation, in which case altered morphogenesis rapidly ensues. In contrast, injury to precursors of bone marrow (*21, 23*) or to male gonadal germinal cells in infant rats is not immediately visible, but is expressed, after a long latent period, in failure to form hematopoietic and spermatogenic cells. An example of a complex chain of developmental events following irradiation is that of the Rongelap people who, exposed to fallout radiation in early childhood, developed atrophy of the thyroid, with consequently impaired body growth and sluggish mental functions (*9*).

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[2] In this chapter, the radiation exposures referred to are usually "acute," that is, of relatively short duration, usually minutes or hours.

Rats exposed during late fetal life to only a few rads a day showed an altered response to typhoid vaccine for several months after birth. In the same period, too, there was diminished phagocytic activity of circulating leukocytes *(33)*.

It has been known that germ cells in the early ovary and testis are especially vulnerable to destruction by radiation at certain stages (7), but only recently have changes in gonadal endocrine functions following irradiation been studied. In laboratory animals, prenatal exposure to a few hundred rads of male or female gonads at several stages of development diminished later hormone secretion by these organs *(4, 15)*. This effect was paralleled by elevated levels of pituitary gonadotropin secretion in females and diminished size in secondary sex organs in the male (*53*).

Virtually all of the effects that have been mentioned are primarily owing to direct irradiation of the developing organism. There are indirect effects on development of the embryo owing to irradiation of the mother that carries it, but the mechanisms are unknown. In one example, normal fertilized rabbit ova transplanted to the uterus of an irradiated mother rabbit showed delayed implantation or failed to develop *(8)*.

IV. Experimental Irradiation of Mammals

Developmental abnormalities resulting from irradiation of the embryos of laboratory animals occur most often when from 50-400 rads are given in the early stages of organogenesis, from the formation of the body axis, first somites, and the neural plate through the laying down of the urogenital system and skeleton. Higher doses are likely to be lethal, whereas low 100's of rads may regularly initiate malformative processes and disturbances of differentiation and growth,—but the affected organism may survive depending on the nature of the abnormalities. These effects become less and less likely to be observed as the dose descends below 100 rads. Permanently altered nerve cells in the brain *(10)* and loss of substantial numbers of germ cells result from as little as 10 rads in infant rats (7), but in neither circumstance has an associated functional deficit been recognized. Exposure of mouse embryos to a few R at various stages, including preimplantation, has been followed by developmental abnormalities which, however, are not distinguishable from those that occur spontaneously and sporadically (*25, 37*). Factors other than radiation may increase the incidence of such "spontaneous" abnormalities; Jacobsen showed, for example, that the incidence of a particular abnormality was greater in winter than in summer. Thus, if the results of control studies done in summer were compared with those of radiation experiments conducted in winter, the harmful effects of radiation might be overestimated; or if the experiments were reversed, radiation effects might be camouflaged. Experiments with a little more than 1 rad per day, over weeks or months, have resulted in life shortening and defective development of gonads and some other organs. The effects of very low levels—millirads per day—of continuous radiation on early development have been little explored experimentally, but evidence at hand has shown no harmful effects (*29, 44*).

There is no uniformly gradual diminution in radiosensitivity as the organism develops. The changing sensitivity to radiation of each organ system has to be considered in its own right. The architectural plan of the urogenital system can be altered only during a relatively short period in early embryonic life, but susceptibility of the skeletal system to malformation waxes and wanes in different parts over a longer period. The brain has the longest period of sensitivity, as it is being formed from primitive "embryonic" cells over a longer time than is any other tissue, this building process extending well into postnatal life in most mammals. The developmental abnormalities observed in man, although almost exclusively externally observed, correspond well to what would be expected on the basis of animal experiments.

V. Effects of Radiation on the Development of Behavior and Other Functions

The ultimate concern about irradiation of the fetus or neonate is for what it may do to the organism's capacity to function, to perform, to behave. In analyzing this complex attribute, function, in man or animal, the investigator must select from a vast number of possible behaviors and other manifestations of function that he might test. Obviously, no single test measures all functions, and generalizations about normality from even a battery of tests are qualified. Only a few rather general correlations have been found between the stage of development at the time of irradiation, morphologic changes in the nervous systems, and the kind of decrement in performance that is observed. In general, investigators have been unable to find changes in various behavioral and functional parameters from exposures below 25 rads. It has been found that certain reflexes and locomotor functions were altered in rats exposed *in utero* to 50 R *(51, 61)*, and more complex motor performances, such as traversing a narrow path, were affected by as little as 25 R *(18)*. Certain behavioral responses in the open field and some forms of conditioning have been altered by 25 R *(19)*. One study *(47)* claimed that exposure of rat fetuses to 1 R at 16 days of gestation affected the rate at which, on reaching adulthood, they became conditioned to experimental circumstances. However, a replication of this study *(20, 60)*, employing the precision of presenting the conditioning stimuli automatically, failed to show effects in rats exposed to less than 100 R.

In assessing the behavioral effects of *in utero* exposure of Japanese children to the atomic bombs, we have no simple, single-measure tests comparable to those which indicated a significant though small diminution in body growth and head size among those closest to the hypocenter. Owing to the lack of appropriate and sensitive tests of brain function, mental retardation has had to be severe to be recognized, even using a number of measures; it was rare below 100 rads and not observed to excess below 25 rads.

VI. Effects of Irradiation from Radionuclides

Radionuclides, ingested medicinally or from fallout, pose special problems in that they are often unevenly transported and distributed to different parts of the body. Because of their special affinities for various tissues, they may localize in certain developing tissues; radioactive iodine concentrates in the thyroid (though not until that organ has reached a certain stage of differentiation), plutonium and strontium in bone, and polonium in kidney. The nature of the compound carrying the nuclide may determine how it is transported in the body and where it is ultimately localized *(46)*. Substances emitting beta or alpha particles irradiate locally their areas of concentration whereas those emitting more penetrating gamma rays have remote effects. The time that the radioactive compound remains in the body (expressed as biological half-life) is a major determinant of its radiation effects. Because juveniles differ from adults in age-related metabolic ways as well as in size, the above factors may be different in the juvenile than in the adult.

The young may differ from adults in susceptibility to injury from radionuclides for a variety of reasons. The skin of the juvenile human and laboratory mammal is more easily injured by radiation than is that of the adult *(9, 26)*. In another example, plutonium and cerium are more readily absorbed from the juvenile gastrointestinal tract that from that of the adult *(3, 27)*.

Some examples illustrate the diversity of radiation effects of radionuclides. The consequences of a concentration of radioactive iodine in the thyroids of Marshallese children has already been discussed. Radioactive phosphorus given to mice and rats in early pregnancy has resulted in embryonic death or malformative growth, depending on the dose and stage of development *(50)*. At later stages, it tended particularly to malform the teeth and jaws *(6)*. Administration of radioactive strontium has retarded growth and caused malformation of the developing fetal skeleton in several mammalian species *(16)*. Plutonium makes the bones of infant and especially juvenile mice become fragile, and spontaneous fractures follow. Plutonium-239 may accumulate in lethal amounts in the yolk sac of early rat embryos; in later gestation, no effect on the fetus has been observed from similar accumulations.

The doses of radionuclides used to produce the pathologic developments just noted were relatively large and carried substantial doses of radiation to the tissues involved. The use of these substances in experiments cannot usually be related directly to the use of radioisotopes in human nuclear medicine. When they are used in man, the amounts of radiation brought to fetal, infant, and juvenile tissues are ordinarily kept at far lower levels than in the experiments.

VII. Estimates of Risks from Irradiation in Early Life

Although, as noted earlier, the variety of possible radiation effects on the developing mammal is almost infinite, numerous experiments have nevertheless shown a predictable orderliness in what happens in any given set of circumstances. Generalizations about risks can be made, based on what has been observed in man and laboratory animals.

In man, diminished body growth, head size, and mental development has been observed after 50 rads to the mother during the earlier months of gestation, and some disturbances of growth may occur after as little as about 25 rads. In experiments with laboratory mammals, in which more precise observation of dose and stage of development is possible, doses as low as 25 rads have produced some impairment of neurologic functions and behavior. Permanent alterations in the morphologic development of some brain neurons and certain other cellular changes have been regularly observed after as little as 10 to 20 rads in fetal and infant rats, but tests thus far have not revealed corresponding changes in function.

The developmental effects of radiation on the embryo and fetus result from the destruction or injury of vast numbers of cells. Innumerable developmental processes are sensitive to radiation, as to other environmental teratogenic agents, and each process has its individual threshold dose-range below which radiation has no visible effect. In radiogenic microcephaly or impaired body growth, the development of the abnormality depends on the summation and interaction of the interruptions of a vast number of processes characteristic of the stage of development, and there are threshold dose-ranges below which these effects are not observed. On the basis of animal experiments, one would expect that a 2-months human fetus that received 200 rads would develop a small malformed brain, with reduced head size; that malformation and diminished brain size would be considerably less marked at 100 rads; and that from 100 rads downward the cellular effects would continue to diminish until alterations of development resulting from them would no longer be measurable.

A particular category of risk estimates relates to therapeutic abortion, which has been recommended after abdominal exposures of 5 to 10 rads in early pregnancy *(34)*. The evidence to be weighed in this regard includes three observations: 1) exposure to radiation as low as 5 rads has produced biological effects (e.g., presence of bilobed lymphocytes) though no clinical disease, in man and experimental animals; 2) though reports conflict, and experimental animal data are lacking, some studies in man (see pp. 160-167) indicate that doses of 1-3 rads, usually late in pregnancy, increase the relative risk of death from cancer in the child during the first 10 years of life by a factor of 1.5 (an increase of 1 cancer death among about 2,000 children per rad); and 3) radiation doses as low as about 25 rads affect the behavior of animals exposed *in utero*. Recent studies suggest that, after intrauterine exposure the gross effects (small head size and mental retardation) seen among atomic-bomb survivors, after substantial doses, may undergo a continuous gradation to small impairment in behavior at lower doses *(68)*. It should be noted that the risk of clinical disease following intrauterine exposure to low doses of radiation is very small, even though cellular damage of indeterminate clinical significance does occur.

VIII. Summary

It has long been recognized that fetal and juvenile mammals are especially sensitive to harm by exposure to ionizing radiation. The mechanisms by which radiation alters the development of structure, behavior, and other functions are extremely complex.

With single brief exposures, the lowest doses observed to bring about these various effects at certain stages in experimental mammals range from a few rads to 50 rads: Occasional germ cells, at certain stages in early life, are killed by a few rads, with no detectable functional effects. Subtle but permanent alterations in nerve cells, at some stages, occur after 10 to 20 rads, but no alterations in behavior are recognized until about 25 rads are given at some stages in prenatal life. The threshold for morphologic alterations in man following irradiation in prenatal life are less precisely known, but observations on the Japanese exposed to atomic bomb radiation place it between 50 and 25 rads to the mother.

There is little information about the effects of chronic low levels of radiation, but experiments have demonstrated that about 1 rad per day, extended over a large part of gestation, is the lowest dose that alters development. Radionuclides tend to be concentrated in certain tissues and act over long periods, but where they can be compared with exposures to atomic bombs and therapeutic x-rays, their effects are similar.

Thus, existing dose-effects data suggest that no effects on growth and development are likely to occur at dose levels compatible with present radiation protection standards.

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CHAPTER VII

SOMATIC EFFECTS OF IONIZING RADIATION

Summary and Conclusions

I. Introduction 85
II. Some Principles Underlying Induction of Somatic Effects 85
III. Cancer Incidence and Radiation Dose 86
IV. Probability of Cancer Induction at Low Doses and Low Dose Rates 87
V. Relative Biological Effectiveness 88
VI. The Linear Hypothesis 89
VII. Risk Estimation 89
VIII. Summary 91
References 91

Appendices to Chapter VII

I. Review of Scientific Bases of Evaluation of Risks of Low-Level Radiation 93
  A. Types of Effects 93
  B. Evidence of the Causal Nature of Associations 93
  C. Dose-Effect Models 95
  D. Ways of Expressing Risk 99

II. Estimates of Risk from Human and Animal Data 100
  A. Cancers 100
    1. Exposure during Childhood or Adult Life 100
      a. Leukemia 100
      b. Radiation-induced Thyroid Cancer 120
      c. Radiation-induced Bone Cancer 125
      d. Skin 132
      e. Breast 136
      f. Lung 145
      g. Other Neoplasms of Specific Types 157
      h. All Cancers Other than Leukemia 160
    2. Cancer following Irradiation before Conception or during Intrauterine Life 160
    3. Total Cancer Risk 167
  B. Mortality from Causes other than Cancer 174
    1. Adult 174
    2. Infant Mortality and Ionizing Radiation 177
  C. Morbidity from Causes other than Cancer 179
    1. Cataracts 179
    2. Central Nervous System Effects 179
    3. Impairment of Fertility 179

III. Analysis of Viewpoints on Record 181
IV. Calculation of Confidence Limits for Risk Estimation 189
V. Radiation Dosimetry of Heavily Irradiated Sites in Patients Treated for Ankylosing Spondylitis 190
VI. Definitions and Notes to Accompany Reference Tables Summarizing Quantitative Data on Carcinogenic Effects of Ionizing Radiation 195

CHAPTER VII

SOMATIC EFFECTS OF IONIZING RADIATION

Summary and Conclusions

I. Introduction

Consideration has been given in this portion of the report to those effects of ionizing radiation that are manifested in exposed individuals themselves (i.e., somatic effects) as contrasted to effects that are manifested in subsequent generations (i.e., genetic, or inherited, effects). Effects of radiation on prenatal and juvenile development are dealt with in Chapter VI.

In reviewing existing knowledge of the effects of interest, the Subcommittee has had access to: (1) previous evaluations by other committees of the National Academy of Sciences of the United States, the National Council on Radiation Protection and Measurements, the International Commission on Radiological Protection, the United Nations Scientific Committee on the Effects of Atomic Radiation, and other panels of experts,[1] (2) published reports available in the world scientific literature; (3) technical documents, including hitherto unavailable data, provided by the Atomic Bomb Casualty Commission, the United States Public Health Service, The Atomic Energy Commission, and other agencies; and (4) private communications from individual scientists, some of which were supplied in response to a widespread appeal to the scientific community for information on the effects of low-level radiation.

In general, the Committee has not considered acute effects of irradiation, since these are already well documented and occur only at dose levels well above those of interest in the setting of protection standards. With few exceptions, the somatic effects we have considered manifest themselves only after an interval of years or decades following irradiation and are indistinguishable from lesions that occur naturally in nonirradiated populations; thus, their relationship to radiation is detectable only in a statistical sense.[2] Thus in any given individual a particular effect cannot be attributed conclusively to radiation, as opposed to some other cause, and the smaller the dose of radiation, the less the likelihood that radiation was in fact a prime cause.

II. Some Principles Underlying Induction of Somatic Effects

To specify numerically the risks of radiation effects under conditions of low-level exposure requires better knowledge than is now available of the mechanisms involved in the production of such effects, of their dose-response relationships, and of the susceptibility of human populations at risk. For none of the effects can the dose-response relationship be defined precisely over a wide range of dose and dose rate, and only for induction of certain types of effects, such as cataracts and impairment of fertility, are the mechanisms of induction known with some precision. For the most part, therefore, estimation of the risks of effects at low dose levels involves extrapolation from observations at higher dose levels, based on assumptions about the nature of the dose-response relationship, the mechanisms involved, the susceptibility of the population at risk, and other factors.[3]

For induction of cataract of the lens and impairment of fertility there is radiobiological and clinical evidence of a nonlinear relationship between effect and dose, these effects presumably depending in large measure on the killing of cells in the lens and gonads, respectively.[4] These considerations imply that there is little or no risk of inducing such effects at doses and dose rates approaching natural background radiation levels. For induction of some tumors, on the other hand, a linear non-threshold dose-effect relationship cannot be excluded from existing data, nor can the possibility that such effects might result from sublethal injury in only one or a few cells of the body.[5] Moreover, evidence available at this time indicates that the most important effect of radiation on the mortality of human populations results from carcinogenesis, including leukemogenesis.[6] Whether in human populations there are radiation effects on mortality from causes other than cancer is still uncertain.[7]

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[1] Federal Radiation Council, 1964; United Nations Scientific Committee on the Effects of Atomic Radiation, 1962, 1964, 1966, 1969; International Commission on Radiological Protection, 1966, 1969; National Council on Radiological Protection and Measurements, 1971 (see references).

[2] See Appendix I A

[3] See Appendix I B

[4] See Appendix II C 1 (cataracts) and II C 3 (impairment of fertility).

In regard to the induction of cancer by ionizing radiation, the following observations are pertinent: (1) the cancers induced by radiation are indistinguishable individually from those occurring naturally, and hence their existence can be inferred only in terms of an excess above the natural incidence; (2) the natural incidence of cancer varies over several orders of magnitude, depending on the type and site of the neoplastic growth, age, sex, and other factors; (3) cancer of any one type occurs with sufficiently low incidence in man that few irradiated populations are large enough to provide convincing quantitative data on the incidence of tumors of any one type or site; (4) the time elapsing between irradiation and the appearance of a clinically detectable neoplasm is characteristically long; i.e., years or even decades; (5) this long induction time complicates the prospective follow-up of irradiated populations for observation of possible tumor development, and it also complicates the retrospective evaluation of cancer patients for possible history of relevant radiation exposure; (6) many of the existing human and animal data on radiation-induced tumors come from populations exposed to internally deposited radionuclides, in which the dose-incidence relation is obscured by marked nonuniformities in the temporal and spatial distribution of radiation; (7) in several other instances, data have been derived from studies of therapeutically irradiated patients, in whom the effects of radiation may have been complicated by effects of the underlying disease itself or of treatments other than radiation; and (8) some of the data concern mortality whereas others concern disease incidence; in the case of cancer it is relevant to differentiate those radiation-induced malignancies that do not greatly alter the death rate (e.g., thyroid carcinoma) from others that in the present state of knowledge are generally fatal (e.g., leukemia).

III. Cancer Incidence and Radiation Dose

Despite the difficulties mentioned, a clear-cut increase in incidence with increasing radiation dose has been documented for several types of cancer in human populations, as well as for many types of neoplasms in experimental animals. Although, with few exceptions, the observed dose-incidence data pertain to relatively high doses (above 50 rem[8] and high dose rates (above 1 rem per minute). The findings for any given neoplasm are reasonably consistent from one irradiated human population to another, suggesting that they may be applicable within limits to the general population for purposes of risk evaluation.[9]

In atomic bomb survivors of Hiroshima and Nagasaki, and in British patients treated with intensive spinal irradiation for ankylosing spondylitis, an increased incidence of all forms of leukemia except the chronic lymphocytic type has been observed. The relationship between the excess in incidence and the radiation dose, as observed at relatively high doses and high dose rates, is consistent with a linear dose-incidence function. For purposes of estimating risk at low doses, it is necessary to extrapolate this linear relationship through the origin at zero dose, on the assumption that the incidence at zero dose is a point on the curve.

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[5] See Appendix I C

[6] See Appendix II A

[7] See Appendix II B

[8] The dose equivalent in rem in strict usage is the product of the absorbed dose in rads and an assigned quality factor, and other necessary modifying factors, and is reserved for use in radiation protection. However, the term "rem" has also been used in the radiological literature to indicate the product of the absorbed dose in rads and RBE, and will sometimes be so used in this report for simplicity. This use of rem is not in strict conformity with definitions of the International Commission on Radiological Units (ICRU). Also, the term "dose" is used broadly to apply not only to the absorbed dose in rads, but to the dose equivalent in rem as well.

[9] See Appendix II A 3

The slope of the fitted straight-line corresponds to a risk of about 1 case of leukemia per 10^6 exposed persons, per year, per rem.[10] The excess in incidence, which was evident within 3-4 years after irradiation, declined within 15 years but still persists at a diminished level in atomic bomb survivors, now 25 years after exposure. Data for other irradiated populations are less quantitative but imply, for high doses, a comparable excess of leukemia per unit of average dose to the bone marrow, despite wide differences in the conditions of exposure. The evidence suggests that susceptibility to induction of leukemia is several times higher in those irradiated *in utero* or during childhood,[11] as well as in those irradiated late in adult life,[10] than in individuals of intermediate ages.

Tumors of the thyroid gland also have been found to show a systematic increase in incidence with increasing dose in irradiated populations.[12] The dose-effect relationship as observed at relatively high doses and high dose rates, like that for leukemia, can be represented by a linear, non-threshold function, corresponding to a risk of 2.5-9.3 cases (not deaths) of cancer per 10^6 exposed children, per year, per rem to the thyroid gland, averaged over the fifth to twenty-fifth years after exposure. Susceptibility to induction of these tumors seems to be several times higher in children than in adults.

For tumors of other types and sites, the existing dose-response data are more limited, and the estimates of risk correspondingly less reliable. For cancer of the lung,[13] the mortality at high doses has been observed to approximate one death per 10^6 exposed persons per year, per rem. For cancer of the breast,[14] the mortality at high doses has been observed to approximate three deaths per 10^6 exposed women per year, per rem. For cancer of the skeleton,[15] the mortality at high doses has been observed to approximate two deaths per 10^7 exposed persons per year, per rem. For cancer of the GI tract including the stomach,[16] the mortality at high doses has been observed to approximate one death per 10^6 persons per year, per rem. Cancer at other sites[17] may contribute a further one death per 10^6 persons per year, per rem. These rates have been derived from the period after irradiation during which an excess in the incidence of these tumors has been evident.

Although cancers of other types have been observed to occur in heavily irradiated tissues (for example, cancer of the skin), there are no quantitative dose-incidence data for such growths comparable to those cited above. The findings imply either that susceptibility to such malignancies is low by comparison with susceptibility to the specific types of cancer mentioned earlier[16] or that the distribution of latent periods for such malignancies extends well beyond the upper limit of 25 years of follow-up achieved for the major long-term studies thus far. In fact, the overall excess mortality from cancer, including leukemia, in irradiated populations can be accounted for largely by the specific types of tumors mentioned above. In the Hiroshima and Nagasaki population, this excess at high doses and dose rates amounts to about 2.5 deaths/10^6/rem/year, averaged over the period[18] in which the excess was observed.[9] Some studies suggest that after prenatal irradiation the overall juvenile cancer mortality may be increased by about 50 cases/10^6/rem/year, averaged over the first 10 years of life; however, the possibility remains that the excess observed in these studies may be dependent on factors other than radiation.[11]

The observed variations in susceptibility to induction of different types of cancer by irradiation, which are apparently unrelated to the marked variations in the natural incidence of the diverse types, make it clear that the concept of a uniform doubling dose of radiation for induction of all types of cancer is invalid.

IV. Probability of Cancer Induction at Low Doses and Low Dose Rates

The dose-mortality figures cited above, which pertain chiefly to human populations exposed at high doses and high dose rates, may be used to estimate the probability of cancer in other populations exposed at lower doses and lower dose rates if it is assumed that the relationship between mortality and dose remains the same irrespective of changes in dose, dose rate, and population at risk. There are cogent radiobiological reasons for doubting that the dose-incidence relationship for cancer induction in man does, in fact, remain constant in the face of such changes, one of which is the widespread occurrence of repair of most other types of radiation injury at low doses and low dose rates, particularly in the case of low-LET radiations.[17] The dose rate characteristic for background radiation (approximately 0.1 rem/year) is one-hundred-million to one-billion times lower than the dose rate at which effects have been observed in most irradiated study populations. At background radiation levels, ionizing events in individual mammalian cell nuclei occur at a rate of much less than one per day, whereas at the higher dose rates mentioned, ionization events occur in cells at a frequency of the order of 2600 per second. This enormous difference may have important implications with respect to the production of radiation damage within cells and its repair at the molecular level. On the basis of the likelihood of such repair, the risk of cancer induction at low doses and low dose rates might be expected to be appreciably smaller per unit dose than at high doses and high dose rates, as has been observed to be the case in certain radiation-induced tumors of experimental animals.[5,10,19] Hence, expectations based on linear extrapolation from the known effects in man of larger doses delivered at high dose rates in the range of rising dose-incidence relationship may well overestimate the risks of low-LET radiation at low dose rates and may, therefore, be regarded as upper limits of risk for low-level low-LET irradiation. The lower limit, depending on the shape of the dose-incidence curve for low-LET radiation and the efficiency of repair processes in counteracting carcinogenic effects, could be appreciably smaller (the possibility of zero is not excluded by the data). On the other hand, because there is greater killing of susceptible cells at high doses and high dose rates, extrapolation based on effects observed under these exposure conditions may be postulated to underestimate the risks of irradiation at low doses and low dose rates.

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[10] See Appendix II A 1 a
[11] See Appendix II A 2
[12] See Appendix II A 1 b
[13] See Appendix II A 1 f
[14] See Appendix II A 1 e
[15] See Appendix II A 1 c
[16] See Appendix II A 1 g
[17] See Appendix II A 3
[18] Follow-up observations on the survivors of the A-bombs dropped on Hiroshima and Nagasaki in 1945 generally began 1 October 1950. Thus, data through 1970 are for the 20-year period five-to-25 years, not 0-to-25 or 0-to-20. Conversion to a rem dose has been done, in this instance, on the assumption that the RBE for neutrons is 5.
[19] See Appendix III.

V. Relative Biological Effectiveness

Another factor complicating extrapolation from the available human data is wide variation in relative biological effectiveness among different types of ionizing radiations. This variation, which depends on differences in the microdistribution of radiation energy, or linear energy transfer (LET), may cause the same total dose to differ in its effects by a factor of 10 or more, depending on the radiation in question. This problem pertains directly to the interpretation of data from several of the principal available sources; namely, atomic bomb survivors of Hiroshima, underground miners exposed to radon gas and its radioactive decay products, and a number of populations with high body burdens of alpha-emitting radionuclides. In the case of Hiroshima, the numbers of survivors are larger, and the statistics correspondingly better, than in the case of Nagasaki; but since the radiations at Hiroshima included an appreciable component of fast neutrons, it is necessary to estimate the relative biological effectiveness (RBE) of this component in order that dose-effect data for the two cities can be appropriately compared. The best estimate of the RBE, at high doses and dose rates, derived from intercomparison of the Hiroshima and Nagasaki data for leukemia, is between 1 and 5,[10] a range of values which is consistent with findings in experimental animals. The value of the RBE, which denotes the ratio between the doses of high-LET and of low-LET radiations for equivalent effects, rises with increase in the spatial concentration of the radiation energy delivered during a given exposure, i.e., with increasing LET.

Also, many radiobiological data indicate that the risk-per-rad of low-LET radiations, such as x rays and gamma rays, decreases to a greater degree with decrease in the dose and dose rate than does the effectiveness of high-LET radiations, which may decrease little if at all. Hence the RBE of high-LET radiations can be expected to increase with decrease in the dose and dose rate. The RBE value of 1-5 for leukemia induction, cited above, may thus be considerably smaller than the RBE value applicable to low doses and dose rates. In this report, values of 1 and 5 have been used for the RBE of neutrons in the Hiroshima experience for the purpose of calculating risk per rem. The data available on human populations exposed to alpha emitters (underground miners, thorotrast-or radium-treated patients, and radium dial painters) indicate that for cancer production alpha particles delivered at relatively low dose rates are 5-10 times more effective per rad average tissue dose than x rays or gamma rays delivered at high dose rates.

VI. The Linear Hypothesis

Although experimental evidence indicates that the dose-effect relationship for x rays and gamma rays may not be a linear function that is invariant with dose and dose rate, the use of a non-linear hypothesis for estimating risks in support of public policy on radiation protection would be impractical in the present state of knowledge, since it would require consideration of individual variations in temporal and spatial distribution of tissue dose, as well as allowance for other variables which cannot be analyzed at this time.

The possible significance of the experimental data is not the only element of uncertainty in interpreting the human data. It is the whole population from birth to death that is to be protected, and no body of human observations provides dose-specific risk estimates for longer than about 25 years. Further, the human fetus may be especially susceptible to radiation leukemogenesis, possibly to carcinogensis generally, but the various studies are not in agreement on the size and nature of the effects of radiation, and no study provides more than 15 years of follow-up. The lifetime cost (to human health) of a particular radiation protection guide may therefore be highly sensitive to the effects of fetal irradiation. Thus, there is no certainty, and in a situation that calls for a careful weighing of costs and benefits it has seemed prudent to present numerical risk estimates for man on the basis of exclusively human data with linear interpolation into the region of low dose, merely indicating at which points the experimental data, or further human observations, might modify such estimates in the future.

At this time, then, the linear hypothesis, which allows the mean tissue dose to be used as the appropriate measure of radiation exposure, provides the only workable approach to numerical estimation of the risk in a population. Further, since there is no means at present of determining the value of the dose-effect slope in the low-dose region of interest, use of the linear extrapolation from data obtained at high doses and dose rates may be justified on pragmatic grounds as a basis for risk estimation.

VII. Risk Estimation

To estimate the actual risk of cancer attributable to a particular increase in the level of exposure of the general population to ionizing radiation would require systematic information on the effect of life-long, low-dose irradiation that is simply not available. However, an approximate calculation at the level of mortality can be made on the basis of the 25-year follow-up studies on A-bomb survivors and on patients treated with intensive spinal irradiation for ankylosing spondylitis. In the Japanese, this excess mortality from all forms of cancer, including leukemia, corresponds to roughly 50 to 78 deaths per 10^6 exposed persons per rem over the 20-year period from 1950-1970, i.e., five to 25 years after exposure. In the spondylitics, the excess mortality corresponds to a cumulative total of roughly 92-165 deaths from cancer per 10^6 persons per rem during the first 27 years after irradiation. If such rates, extrapolated to low-dose levels without allowance for the possible dependence of the effect of dose and dose rate, are assumed to apply generally, then exposure of the U.S. population of about 200 million persons to an additional 0.1 rem during one year (approximately equivalent to a doubling of irradiation from background sources), for example, could be expected to cause 1350-3300 deaths from cancer during the 25 years following irradiation, or about 50 to 130 deaths per year. *Continual* exposure of the population to the additional 0.1 rem per year could be expected ultimately to cause 1350 to 3300 deaths *annually*, provided that the effect of a given increment of dose did not persist beyond 25 years after exposure. However, use of a factor, if known for man, to take into account the influence of dose and dose rate on the dose-effect relationship might reduce these estimates appreciably.

When consideration is given to the full cumulative experience of an entire population, more specific attention should be paid to age at exposure, duration of latency, and to the size and duration of the effect; and calculations should be made on the basis of the actual age distribution of the population and the presently-observed age-specific mortality from leukemia and other forms of cancer. Since virtually all human data derive from much higher doses and dose rates than those of present interest, and do not extend beyond 25 years of systematic follow-up, the Subcommittee has considered it advisable to illustrate the uncertainty that must necessarily, at this time, characterize estimates of the effect of a particular level of chronic low-dose irradiation on the entire population by choosing, for both leukemia and all other cancers combined, a range of values for each parameter entering into such estimates. The estimation process, which is fully described in the report,[9] yields figures for the annual number of cancer deaths, without allowance for the influence of dose rate. These figures range from roughly 2,000 to 9,000, depending on the values selected for the parameters in question and on the choice of model used. The Subcommittee considers the most likely estimate from this type of model to be approximately 3000-4000, which is equivalent to roughly 1% of the spontaneous cancer deaths per year. (Since 0.1 rem per year approximates the average value of the natural background radiation level in the U.S., these figures represent the number of cancer deaths attributable to irradiation from natural sources). Because a linear extrapolation model has been used in the calculations, the number of cancer deaths attributable to any dose other than 0.1 rem/year can be estimated by simple multiplication; however, it must be borne in mind that the foregoing estimates of mortality from radiation exposure may be too high, or too low, for a variety of reasons: (1) the carcinogenic effects of a given dose of low-LET radiation may be lower at low dose rates than at the high dose rates on which these estimates have been based; (2) conversely, the carcinogenic effects per unit dose may be higher at low doses and low dose rates, owing to less killing of cells susceptible to cancer induction; (3) insofar as high dose data have provided a basis for the estimates given here, the risks may have been overestimated, owing to side effects at high dose levels which can enhance the carcinogenic action of radiation under certain conditions; (4) longer periods of follow-up may lead to estimates of risk that differ in magnitude from those above; (5) none of the estimates of risk used by the Committee derives from a sufficiently large experience to be free of sampling variation; i.e., the data on most radiation-induced tumors are too scanty to allow construction of dose-incidence curves adequate for extrapolation; (6) uncertainty attaches to the RBE values which must presently be used for alpha and neutron radiations; and (7) further uncertainty attaches to the relevant organ or tissue dose, owing to attenuation of the radiation with depth in the body and to other sources of nonuniformity in the spatial distribution of the dose.

The figures presented in the foregoing are not to be taken as precise estimates of risk since they are based on the incomplete evidence presently available. Moreover, the values are based on mortality data and do not, therefore, represent the number of individuals affected. If expressed in terms of incidence, including nonfatal cancers, estimates of risk could be higher by a factor of roughly 2. Follow-up studies are just now attaining sufficient scope to provide information on the magnitude and duration of the overall cancer risk in irradiated populations. Nevertheless, these estimates illustrate the gravity of the problem facing those who must set radiation protection guides or standards. It is essential not only that the mean dose of radiation from all manmade sources that is received by the population be as low as is practicable, but that the dose to the individual also be minimized.

Whether there are other somatic effects that deserve to be considered in the same category with cancer in evaluating the risks of low-level irradiation remains to be determined. For those effects that may be conceived to fall into this category, however—induction of cataracts,[4] life-shortening from causes other than cancer,[7] and impairment of fertility[4] — existing dose-effect data suggest these are not likely to occur at dose levels compatible with present radiation protection guides. Hence, it seems reasonable to limit consideration to cancer alone for the purpose of this evaluation.

Despite the incompleteness of the data, the evaluation of risks based on the approach summarized above affords a rational means of appraising the adequacy of radiation protection standards in perspective with other factors to be considered in the relevant cost-benefit analysis. It is essential, however, that these problems remain under constant review, to observe, record, and evaluate all relevant new data, in order to insure that the estimation of risk from radiation in exposed populations be as precise as possible.

VIII. Summary

Cancer induction is considered to be the only source of somatic risk that needs to be taken into account in setting radiation protection standards for the general population. Despite many uncertainties, an approximate estimate of overall cancer mortality can be made on the basis of follow-up studies on Japanese atomic bomb survivors and patients treated with radiation for diseases other than cancer. In these populations, the excess mortality from all forms of cancer corresponds to roughly 50-165 deaths per 10^6 persons per rem during the first 25-27 years after irradiation. By extrapolation, it can be estimated that the number of deaths per 0.17 rem per year in the entire U.S. population might range roughly from 3,000 to 15,000 with the most likely value falling in the range of 5,000 to 7,000 (or 3,500 per 0.1 rem per year).

It is emphasized that the risk estimates lack precision but do indicate that the mean dose both to the population and to each individual must be kept as low as practicable.

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APPENDICES TO CHAPTER VII

Appendix I. Review of Scientific Bases of Evaluation of Risks of Low-Level Radiation

A. Types of Effects

Aside from cytologic (*1*, *2*) and cytogenetic (*3*) abnormalities, the pathologic significance of which is unknown, no radiation injuries have been documented in man or other mammals under exposure conditions compatible with existing radiation protection guides. Nevertheless, the possibility of certain somatic effects of low-level irradiation cannot be excluded. These include neoplasms, opacities of the lens of the eye, impairment of fertility, defective development of the fetus, and life shortening (*4*, *5*). Of these, cancer is the chief concern, because it usually involves greater detriment to an affected individual than do any of the others and because the risk of cancer may conceivably be increased by smaller amounts of radiation than are required to cause any of the other effects in question (*5*). In this report, therefore, primary emphasis is placed on evaluating the possible risks of cancer associated with low-level irradiation.

Complete evaluation of the risk of cancer, or of any other somatic effect, requires knowledge of the dose-effect relation. Because, however, dose-effect data for all the effects of interest are fragmentary, particularly under conditions of low-level irradiation, the evaluation must be based largely on extrapolation from data that have become available through studies of the effects of larger amounts of radiation on human and animal populations. Analysis of these data entails assessment of the nature of the association between exposure to radiation and the effects in question, interpreted in the light of existing knowledge of the possible mechanisms of production of such effects.

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B. Evidence of the Causal Nature of Associations

In the field of human radiobiology there are many situations in which the question at issue is not whether an association exists between radiation exposure and a particular disease or other manifestation, but whether the association is a causal one. That is to say, whether or not reduction or elimination of the radiation exposure *per se* would be followed by a reduction in frequency of the disease.

Contrary to widespread belief, evaluation of the causal nature of an observed association is a statistical problem, and does not involve the concept of "proof" in any definitive sense. The evaluation requires the assembly of information and concepts from many different sources and their integration into an overall estimate of the *likelihood* that the association is or is not causal. Where controversy exists, attention should primarily be focused not on whether the association is "proven", but on the limitations, the adequacy of the data, the lack of design and corresponding artifacts, and finally the choice of the appropriate "control" for the

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situation. In this process of assembly and integration of data there may come a point at which it becomes - for the purpose of making decisions or taking actions of practical import - more prudent to act as though the association were causal, than to continue to regard it as non-causal. Where controversy exists, it should be focussed on whether or not currently available data lead us to this point, rather than on the unanswerable question of whether the causal nature of the association is or is not "proven". It is important to recognize that both the evaluation of individual pieces of evidence and the relative weights assigned to evidence of different kinds contain substantial elements of subjectivity, and that there are few biologic issues on which belief in the strength of the evidence of causality does not vary widely among experts in the field.

The kinds of evidence pertinent to evaluation of causality have been the subject of philosophical discourse for many centuries (recent reviews are in *1* and *2*). When it exists, the strongest evidence is usually derived from observation of the sequelae of deliberately and randomly assigning individuals to different levels of the exposure. As is so obvious in the field of radiobiology, the limitation of this method is in the very few problems to which it can be applied. In the absence of experimental evidence, three types of consideration are useful:

1. *Time sequence.* For radiation to be considered a cause of a particular disease, it is clear that the radiation must precede the appearance of the disease.
2. *Strength of the association.* The "stronger" the association (that is to say, for example, the higher the ratio of the incidence of the disease following a given dose of radiation to the incidence of the disease at lower doses or in the absence of prior radiation), the more likely is the association to be causal.
3. *Consonance with existing knowledge.* Belief in the causal nature of an association is supported by knowledge of a cellular or subcellular mechanism that makes a causal relationship reasonable in the light of existing knowledge in relevant sciences, by analogy from experimental work in other species, and by evidence that the distribution of the disease in populations follows the distribution of the supposed cause. Evidence obtained through exclusion may also be pertinent - the more extensive the efforts that have been made to identify non-causal explanations of an association, the more one is likely to believe, if these efforts have been unsuccessful, that the association is causal.

In most situations in which the existence of a causal association has become widely accepted on the basis of non-experimental evidence (e.g., fecal contamination of water and cholera, cigarette smoking and lung cancer, high doses of radiation and leukemia) the second type of consideration - strength of the association - has played a major role, for all these associations have involved "relative risks" (ratios of risk in exposed to risk in non-exposed) of the order of 10 or more. This poses a particular problem in regard to the effects of very low doses of radiation, for it is clear that if, for example, cancer were in fact increased in persons exposed to very small doses, the overall rate in such persons would probably be only slightly higher than that in non-exposed persons. Indeed, even the demonstration that such an association existed - much less evaluation of its causal implications - may be beyond the realm of feasibility, although if it did exist, such an increase in rates would be important because of the very large number of people exposed to low doses of radiation. It is extremely difficult to exclude non-causal explanations of relatively small increases in disease rates, and in this particular situation considerable weight must be placed on the types of consideration in the third category, namely, consonance with other knowledge. At the present time, evaluation of effects in man of low doses of radiation must depend heavily on consideration of possible mechanisms and on extrapolation across doses and, sometimes, species.

Consideration of radiation carcinogenesis in human populations exposed to low doses of ionizing radiation is complicated by noteworthy difficulties: (1) such large populations must be studied to obtain precise data on the incidence of neoplasms at any given site that few irradiated populations are large enough to yield quantitative dose-incidence data for any one type of neoplasm; (2) the long latent period intervening between irradiation and the appearance of many neoplasms hampers the follow-up of exposed individuals in prospective studies and hampers evaluation of the exposure history of individuals in retrospective studies; (3) because of the long duration of the latent period and the limited follow-up of irradiated populations to date, it is not yet possible to estimate the risks of radiation-induced cancer for the entire life span; (4) many of the existing data are based on patients who were exposed to radiation for medical purposes and whose risk of cancer may have been influenced by other treatments or by underlying disease itself, complicating the applicability of such data to the general population; (5) because the natural incidence of cancer varies widely from one organ to another and is influenced by genetic background, age, sex, geographic location, diet, socio-economic factors, and other variables, the action of which is not fully understood, dose-incidence data derived from one population may not be directly applicable to another.

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C. Dose-Effect Models

The following considerations pertain primarily to the induction of cancer, but some of the general principles are also pertinent to the induction of non-neoplastic lesions.

1. General Aspects of the Causation of Cancer

Although the mechanisms of carcinogenesis, or of radiation carcinogenesis in particular, are not fully known, available information implies that most, if not all, types of cancer develop as a result of the combined effects of multiple factors. These causative factors may include: prezygotic (inherited) mutations of chromosomal aberrations, which can spread during development to many kinds of cells; somatic cell mutations or chromosomal aberrations, which can be acquired at any time after conception; changes resulting from the action of viruses; and changes in systemic growth factors (e.g., depressed immune competence, hormonal imbalance) and in local tissue regulation (disorganization, damage), such as may result from diseases other than cancer or from **advancing age (*1*).**

Although point mutations, chromosomal aberrations, and other changes at the cellular and molecular level may require only small doses, tissue disorganization and gross disturbances in physiology are unlikely without larger doses (*2*).

Of the many types of changes which radiation can cause in cells or tissues, none is considered to be unique for radiation. Many, if not all, such changes can presumably result from a variety of other agents.

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2. The Question of a Threshold Dose for Carcinogenesis

The amount of radiation required to induce cancer in an individual (individual dose threshold) can be assumed to be a variable, dependent upon the extent to which causes other than the radiation contribute to the total carcinogenic process. It is the distribution of individual dose thresholds for any particular population that will determine the dose-effect function for that population. The term "threshold dose" for carcinogenesis is a heuristic concept used to denote the radiation dose required to cause cancer in the most susceptible (to radiation) individual in the population. It is taken to be an **absolute value below which cancer will not be induced by radiation, and at or above which it will be induced in susceptible individuals.**

The concept is an attractive one because there are well-confirmed non-linear responses to radiation in the experimental literature. In radiation carcinogenesis the concept may have value in the design and interpretation of experiments, but its applicability to the setting of guidelines for human exposure is highly questionable. There is no sufficient theory of radiation carcinogenesis from which the concept may be deduced, and an empirical demonstration has not been made. Most human data apply to high doses and high dose rates, and to utilize these data in developing guidelines for human exposure at low doses and low-dose rates requires interpolation between the region of high dose and zero dose. The significance of the threshold-dose concept enters at the point where one asks: How is the interpolation to be done? Linear models are easy to apply and give clear-cut estimates - but provide estimates of non-zero risk even at the lowest portion of the dose-scale Some human populations are so large that even very small linear estimates of risk, in the region of dose prescribed by current guidelines, yield finite estimates of induced cancers, i.e., deaths. These estimates of risk are beyond empirical demonstration. It is unlikely that the presence or absence of a true threshold for cancer in human populations can be proved. If the intent of authorities is to minimize the loss of life that radiation exposure may entail, they must, indeed, be guided by such estimates, and will not rely on notions of a threshold.

3. *Dose Rate and Relevant Dose in Carcinogenesis*

Reduction of the dose rate by protraction or fractionation of exposure over extended periods of time generally permits substantial recovery of cells and tissues from radiation damage, at least in the case of low-LET radiations under experimental conditions. Whether the induction of cancer is correspondingly affected may be expected to depend on the effectiveness of the total dose when delivered at a high dose rate and on any change in susceptibility that might be associated with increase in the age at irradiation resulting from the prolongation of exposure. Reduction of the dose rate in delivering a dose at a very high level has been observed to increase its oncogenic effectiveness in experimental animals (*1*), presumably by reducing lethal damage of cells and tissues, whereas reduction of the dose rate in delivering a smaller, suboptimal dose has been observed experimentally to reduce its carcinogenic effectiveness (*2*).

When irradiation is prolonged, by protraction or fractionation, the portion of the total accumulated dose which is relevant (effective) for the induction of cancer is uncertain. If irradiation is prolonged beyond the point at which the cancer is induced, the corresponding part of the remaining accumulated dose will be irrelevant as far as the induction of cancer is concerned, although it might conceivably influence the length of the latent period (*2*).

Nonuniformity in the spatial distribution of dose within tissue (microdistribution) and nonuniformity in the distribution of dose among individuals within a population are other factors which may complicate determination of the dose that is relevant for an observed induction of cancer. For example, the existence of "hot spots" in the distribution of radioactive isotopes in tissue raises the question of whether the relevant carcinogenic dose is the dose in or around the "hot spots", the dose in regions of more diffuse distribution of the isotopes, the average dose for the whole organ, or the corresponding dose to those particular anatomical types of cells within the organ that are considered to be the source of the cancer (*3*).

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4. *Dose-Effect Relationship*

For cancers induced experimentally by irradiation, there is generally an increase in incidence and a decrease in latent period as the dose is increased within a certain dose range (*1*). Above this range, the probability of cancer induction tends to reach a maximum and then decrease ("turn-down") with further increase in the dose. The turning-down of the dose-incidence curve at high dose levels has been attributed to excessive cell killing, tissue destruction, and shortening of life span from causes other than the cancer in question. Experimental data for many dose intervals over a wide range often give rise to a sigmoid curve, with a rising concave portion followed by a rising, fairly linear portion, followed by a plateau, and then a falling portion in the region of highest dose.

When only parts or combined fragments of the total dose-incidence curve are observed and used to extrapolate to the low-dose range for which there are no adequate, concrete data, as the basis for estimating the risk of low-level irradiation for man, assumptions must be made concerning the shape of the curve in the low-dose region. In concept, this will depend on the particular carcinogenic mechanisms, the influence of dose rate, the distribution of individual thresholds within the population, and the latent periods for carcinogenic effects as influenced by dose and dose rate. In practice, these factors are little known.

In regard to cellular neoplastic initiation in the carcinogenic mechanisms, the shapes of dose-response curves for genetic effects of radiation may be pertinent to the consideration of dose-response curves for leukemia and other neoplasia. The induction of neoplasia by radiation may well involve direct injury to individual cells or groups of cells, and possibly to the genetic apparatus of such cells. Thus, the lesion produced in somatic cells may be analogous to that produced in germ cells, i.e., a "somatic mutation" of some type may be involved in the induction of neoplasia. In the female mouse, a reduction in dose rate has been observed to reduce the number of mutations to that seen in nonexposed controls. In the male mouse, a less marked dose-rate effect was seen, the slope of the dose-effect curve at low dose rates being one-third to one-fourth of that seen at high dose rates (See Chapter V, p. 52).

Figure 1 is a schematic representation of observed (solid parts of lines) and unobserved (dashed parts of lines) portions of various incomplete experimental dose-response curves for both leukemia and genetic effects. Curve "a" (solid line portion) represents observations made at high doses and high dose-rates and is in itself insufficient to determine the functional form of the relationship, particularly in the region of low dose. The observed (solid portion) straight line "a" is consistent with the data, and so is the observed (solid portion) straight line "b" but "a" extrapolates linearly to zero dose and zero effect, while "b" is curvilinear and does not. With reduced dose rate, the observations may be represented in some systems by "c" (e.g., genetic effects in the male mouse) or by "d" (e.g., genetic effects in the female mouse).

The available data on radiation-induced cancer in man are relatively scanty, the conditions of exposure nonuniform and uncertain, the irradiated samples highly heterogeneous, the controls uncertainly or crudely matched, the observations confined to limited (high) or ill-defined ranges of dose, dose rate, and fraction of total possible post-exposure risk time, and the effects of variables other than radiation incompletely known.

In view of the gaps in our understanding of radiation carcinogenesis in man, and in view of its more conservative implications, the linear, nonthreshold hypothesis warrants use in determining public policy on radiation protection; however, explicit explanation and qualification of the assumptions and procedures involved in such risk estimates are called for to prevent their acceptance as scientific dogma. Furthermore, the linear hypothesis is the only one which permits the selection of the mean accumulated tissue dose to characterize the radiation exposure of a group under conditions of nonuniform exposure and exposure rate. The mean accumulated tissue dose is the only practical quantity that can be used to estimate the risk of cancer in such populations until the influence of the many interacting variables can be better specified (*2*).

There is also some theoretical and logical basis for use of the linear hypothesis at low dose levels. If the dose and dose rate are small (e.g., at maximal permissible levels of low-LET radiation), the spatial and temporal separation of ionizations is sufficiently large so that one would expect effects to be caused principally by "single track" radiation, and that interactions of radiation tracks within cells would be so improbable as to be negligible. This argument implies a linear dose-effect relationship for molecular and cellular effects at low dose levels, even though larger doses, which may cause "multi-track" interactions at the cellular level or at the tissue level, may be associated with a nonlinear relationship.

In the attempt to derive risk estimates with which to set dose limits for protection against radiation carcinogenesis, it is necessary to consider the range of dose and dose rate over which dose-effect data can provide a reasonably valid slope for extrapolation to low dose levels. If the slope (rate of increase in incidence with increasing dose) to be used for linear ex-

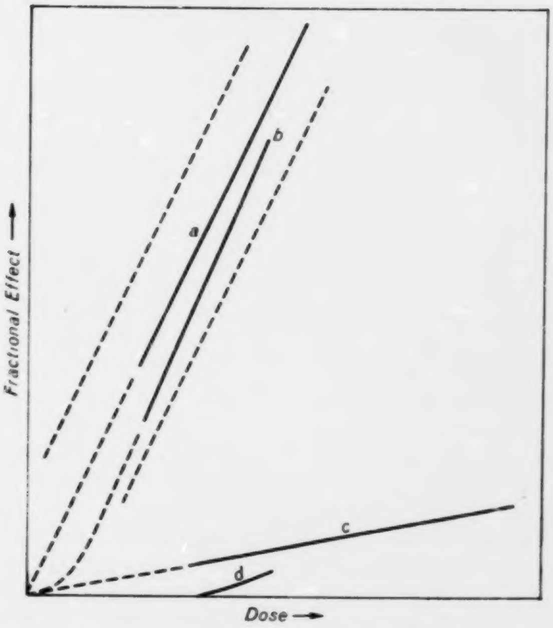

Fig. 1. Hypothetical dose-response curves for leukemia and genetic effects.
Solid lines = observed; dashed extension of solid lines = unobserved.
Lines "a" and "b": possible dose-response curves at high doses and dose rates
Line "c" = genetic effects in the male mouse
Line "d" = genetic effects in the female mouse
Parallel dashed lines = rough limits of error for lines a and b.

trapolation to low dose levels is obtained by interpolation between effects observed at zero dose and those observed in the most rapidly rising segment of the curve, the estimated risk per unit dose at the low dose levels is likely to overestimate the real risk at low doses. However, if the slope for linear extrapolation is obtained by interpolation between effects observed at zero dose and those observed within the high dose range of the dose-effect curve, where the doses exceed the maximum effective induction dose, the risk per unit dose at low dose levels may be underestimated. Estimates of risk are, of course, not scientifically reliable except in the range of observations from which they are derived and under corresponding conditions of exposure.

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D. Ways of Expressing Risk

Estimates of risk may be expressed in absolute terms or in relative (comparative) terms. The absolute risk is the excess of risk due to irradiation. In practice, this is the *difference* between the risk in the irradiated population and the risk in the nonirradiated population. For example, under the linear dose-incidence model, the absolute risk may be expressed as the number of excess (radiation-related) cases of cancer per unit of time in an exposed population of given size per unit of dose (e.g., 1 case/10^6 exposed persons/year/rad).

The relative risk is the *ratio* between the risk in the irradiated population and the risk in the nonirradiated population. It is usually stated as a multiple of the natural risk. The doubling dose, i.e., the dose that will double the standard (natural) risk, is a special example of a calculation of relative risk.

Absolute risk estimates are generally more useful for purposes of radiation protection than are relative risk estimates, because they specify directly the number of persons affected (*1*). On the other hand, if the risk due to radiation were found to increase in proportion to the natural risk, then the relative risk would provide the more appropriate estimate. Since the existing knowledge of radiation carcinogenesis is not always sufficient to indicate which type of estimate applies best in a given situation (*2*), both the absolute risk (where possible) and the relative risk are given in this report. Either type of estimate when applied to dose levels for which human data are lacking involves assumptions concerning the dose-effect relationship. Either type of estimate also involves assumptions concerning the distribution of risk with time after irradiation — namely, the time elapsing before the risk becomes elevated ("latent-period") — since pertinent information for most types of cancer in human populations is fragmentary as yet.

As suggested by the ICRP (*3*), the expression of risk estimates in absolute terms — for example, 2 cases per million exposed people per year per rem — might be misinterpreted as implying considerably greater accuracy than the facts justify. For this reason, estimates are sometimes expressed in terms of "orders of risk", e.g., 1 to 10 cases/10^6/year/rad is a 6th order risk.

In the tables prepared by the Committee to summarize the human data, use is made of 80 percent confidence intervals on absolute risk estimates to facilitate comparison of the data from different studies and not to imply greater accuracy than is warranted.

In order to minimize their misinterpretation and misuse, numerical risk estimates should regularly be accompanied by the following qualifying information:

(a) Range of doses, dose rates, and exposure conditions on which the risk estimate is based and for which it is, therefore, scientifically valid.
(b) Any biomedical conditions or indications for irradiation affecting the population for which the risk estimate is scientifically valid.
(c) Age range (at irradiation) for which the risk estimate is scientifically valid.
(d) Sex for which the risk estimate is scientifically valid.
(e) Years of observation or person-years at risk for which the estimated average annual risk or total risk are valid. The expression of risk on an annual basis averaged over a short period may give an

underestimation of the lifetime risk for cancers with a longer modal latent period, or may give an overestimation of lifetime risk for cancers with a short modal latent period. One of the most serious problems is the fact that existing knowledge of cancer induction in man is based on a limited number of years after exposure, and information is lacking about risk during later years when the natural cancer incidence increases greatly.

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Appendix II. Estimates of Risk from Human and Animal Data

A. Cancers

1. Exposure during Childhood or Adult Life

a. Leukemia

Introduction

Although the mechanism of leukemia induction remains unknown, radiation leukemogenesis has been empirically established by experimental studies and by numerous epidemiologic surveys on man. Previous estimates of the risk of radiation-induced leukemia in man have been made principally from data on Japanese survivors of the atomic bombings of Hiroshima and Nagasaki, and on patients in Great Britain who were given therapeutic x-irradiation of the spine for ankylosing spondylitis (*1, 2*). The dose-effect curves for both of these experiences have been taken to be consistent with a linear increase in incidence with dose, from which the excess risk from radiation at high doses and high dose rates has been inferred to be of the order of $20/10^6$/rad over a period of 20 to 25 years following exposure to 100 rem or more, or 1-2 cases/10^6/rad/year (*1, 2*). This estimate was considered to represent average risk for exposure at high doses and dose rates; linear extrapolation of the curve downward (or interpolation if zero effect at zero dose is assumed to represent a point on the curve) was considered to represent an upper limit of risk at low doses and dose rates. The fact that an appreciable part of the total dose in Hiroshima was due to neutrons was not taken into account in the estimate cited, nor was any numerical factor introduced to adjust the risk for exposure at low dose rates.

The A-bomb Survivors

The data from Hiroshima and Nagasaki have since been updated and reanalyzed, at the level of incidence for the period October 1950 to September 1966 (*3*), and at the level of mortality of October 1950 to December 1970 (*4*), on the basis of improved (T-65) estimates of both neutron and gamma doses in the two cities[1]. These new appraisals, from the Atomic Bomb Casualty

[1] Some of the most useful data available for the evaluation of the late effects of radiation on man come from the Atomic Bomb Casualty Commission: The population of A-bomb survivors is large and received doses ranging from the trivial to the near lethal; estimated doses are available for almost all; the population is relatively unselected (except for mortality at the upper end of the dose range), in contrast to series arising from therapy administered for pre-existing disease or from occupational exposure.

Although the ABCC data are probably among the best available, they are subject to certain constraints and qualifications. Most important is the fact that, as in all large human radiation studies, since there was no randomization of survivors to dose, there is no guarantee that high- and zero-dose survivors are actually alike in all respects other than the radiation doses received. The radiation dose depended on the place where a survivor was located at the instant the bomb was detonated; for women, this was usually the place of residence, for men often the place of employment. Survivors at different distances are not exactly alike with respect to patterns of employment, age, or sex. Although these factors can be allowed for explicitly in statistical analysis, there remains the possibility that other factors, not measured, also distinguish survivors in different dose classes and are responsible for some of the observed differences in subsequent experience.

The radiation experienced by the survivors was, of course, received at a very high dose rate. The problems involved in extrapolating data which pertain to large doses at a high dose rate to small doses at a low rate are considered elsewhere in this report. Similarly, the fact that in Hiroshima there was a considerable admixture of neutrons in the radiation which emanated from the bomb raises a question about the relative biological effectiveness of highly energetic neutrons as compared with gamma radiation.

Commission (ABCC) in Japan, provide the first truly dose-specific analysis of the leukemia experience of the A-bomb survivors. Even second-generation dose estimates and 25 years of surveillance of the A-bomb survivors do not, however, provide definite answers to all the important questions relating to the influence of ionizing radiation on the empirically determined risk of leukemia, entirely apart from questions of etiologic mechanisms. This is because the variables capable of influencing that risk are numerous and are not all represented in the experience of A-bomb survivors (e.g., dose rate), and because, for the region of low dose, even the population of A-bomb survivors is not large enough to permit accurate assessment of the presumably low risks in question.

Certainly by 1950, and perhaps as early as 1948, an excess of leukemia was apparent in A-bomb survivors (*6*) so that the period of latency of radiation-induced leukemia can safely be regarded as less than 5 years following whole-body, single-dose exposure over a wide range of dose, for both Nagasaki (essentially gamma radiation alone) and for Hiroshima (mixed gamma rays and neutrons). In 1960, Heyssel et al. (*7*) showed that the incidence of leukemia in A-bomb survivors had already exceeded their lifetime expectation at the rates then prevailing in Japan. In 1965-1970, 20-25 years after exposure, the excess was still apparent (*4*), but greatly reduced from the peak incidence in 1951; acute forms of leukemia were more clearly in excess than chronic, however, in the period of 1960-1966 (*3*).

Although the Leukemia Registry maintained by ABCC in both cities with the aid of the medical schools, hospitals, and physicians of the community, included 1,360 cases on 30 June 1967, only 430 were A-bomb survivors, and only 117 were definite or probable cases within the ABCC Master Sample of 117,000 survivors on 1 October 1950, with onset between 1 October 1950 and 30 September 1966, and with known dose (Table a-1). The current (T-65) dosimetry (*8, 9*) like that used previously (*6,7*), leads to

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All doses of radiation received by the exposed Japanese have been corrected for shielding, and refer to the dose "free in air" at a point corresponding to the center of the body (technically, the kerma in air at a location corresponding to the center of the body). Depth-dose curves have been obtained for gamma and neutron radiations from atomic weapons detonated in field studies (*5*). The dose of gamma radiation, referenced to the dose "free in air", falls off from 100 percent on the side of the body trunk nearest the weapon to about 65 percent on the opposite side of the body. The neutron dose, also referenced to the "air dose", is about 75 percent at the body surface nearest the weapon, of the order of 15 percent or 20 percent at the midline and approximately 40 percent on the side most distant from the weapon. These considerations should in principle be taken into account in specifying the absorbed dose to the bone marrow and other tissues in the body. However, depth-dose relationships differ appreciably depending upon the precise geometry of exposure. Since this is highly variable and in fact unknown in many instances, it was deemed impractical at present to give values for absorbed dose. Therefore, all doses are given only in terms of the "air dose".

An important feature of the Hiroshima and Nagasaki experience is that, in fact, the largest part of the energy released by the bombs was in the form of heat and blast. Many of the survivors were burned, either by radiant heat from the fire-ball or by the fires that engulfed the cities directly after the bombings. Homes were destroyed; food was short; living patterns were profoundly disrupted. The influence of this concatenation of disasters upon the subsequent health of the survivors is unknowable. The issue is further complicated by the possibility that, at least to some degree, the less hardy members of the population had higher mortality during the first few weeks after the bombings, from either disease or radiation effects. Thus the survivors may on the one hand be selected as among the most fit of the bombed population but on the other hand have suffered a variety of experiences all combining to reduce their future fitness.

Two classes of "controls" are employed in the ABCC data: persons who came into the cities after the bombings (so called Not-in-City or NIC group) and survivors who were in the cities, but at such great distances or protected by so much shielding that their estimated doses were small. Neither group is ideal as a control, the NIC group because the immigrants are clearly distinguishable from survivors according to many socioeconomic and perhaps health factors which undoubtedly affect subsequent morbidity and mortality; the low-dose survivors because they may include some small fraction who actually did receive large doses that some relatively small errors in dosimetry are potentially less disturbing than the known large differences that mark the NIC group.
respect to occupation, social class, and perhaps other factors as well.

The Subcommittee judges that the more suitable comparison group consists of the low-dose survivors, those who received doses estimated to be less than ten rads, believing that some relatively small contamination on the side of dosimetry is potentially less disturbing than the known large differences that mark the NIC group.

The data coming from the ABCC Master Sample are concerned with morbidity and mortality that occurred only after October 1950, that is, about five years after the bombings. This deficiency is of little real importance for the study of solid tumors in relation to radiation, since the evidence is good that for such tumors latent periods exceed five years. Leukemia, however, has a shorter latent period, and for the complete study of radiation leukemogenesis, recourse must be had to the whole data of the Hiroshima and Nagasaki Leukemia Registries, not merely that part which concerns the Master Sample.

Table a-1

Incidence of Leukemia in A-bomb Survivors, by T-65 Dose and by City, 1950-1966, ABCC Master Sample (from Ref. 3).

T-65 dose (rads)							
	Median values					Leukemia	
Range	Gamma	Neutron	Total	No. of subjects	Thousands of person-years	Cases	Rate
				Hiroshima			
300+	323	112	427	825	12.1	17	140.5
200-299	185	49	241	606	9.0	5	55.6
100-199	105	27	131	1,652	24.1	10	41.5
50-99	56	13	68	2,611	38.3	7	18.3
20-49	26	5	30	4,555	67.0	14	20.9
5-19	8	2	10	10,541	156.0	8	5.1
Under 5	0	0	0	62,515	915.1	27	3.0
TOTAL	-	-	-	83,305	1,222.7	88	7.2
				Nagasaki			
300+	417	7	427	566	8.4	6	71.4
200-299	238	3	240	693	10.4	6	57.7
100-199	145	2	146	1,174	17.7	3	16.9
50-99	69	0	69	1,173	17.6	0	0
20-49	31	0	31	1,354	20.0	0	0
5-19	10	0	10	4,501	66.3	2	3.0
Under 5	0	0	0	20,403	297.2	12	4.0
TOTAL	-	-	-	29,864	437.6	29	6.6

different dose-response curves for the two cities, but the curve for Hiroshima now appears steeper than that for Nagasaki (Figure a-1). Apart from questions of possible error in the dosimetry which cannot be entirely excluded (*10*), and of genetic and other differences between the populations of the two cities, the primary factor differentiating the two cities is the quality of the radiation received, with neutrons playing an important role in Hiroshima (Table a-1) and almost none in Nagasaki. The dose-response curve for Hiroshima can be represented by a linear function, although other relationships cannot be excluded. If gamma rays and neutrons are assumed to be equal in relative biological effectiveness (RBE) for induction of leukemia, and the dose-response curve for Hiroshima is assumed to be linear, the excess of leukemia corresponds to about 3 cases/10^6/year/rad of whole-body external radiation (*3*). A variety of curves, including a straight line, can be fitted to the smaller Nagasaki experience. Hence one cannot conclude, from these data alone, that the dose-response effect of gamma radiation in man is or is not linear. On the linear assumption, and with excess cases at all dose-levels pooled and divided by person-year rads, the data of Ishimaru et al. suggest that excess leukemia cases in Nagasaki amount to about one per 10^6/year/rad. In Hiroshima a significant excess of leukemia was seen at and above the dose range of 20-49 rads. In Nagasaki, on the other hand, the excess was not significant below 100 rads. The paucity of cases in the interval 20-99 rads may well result from a combination of sampling variation, on the one hand, and the restraints imposed by this particular analysis, especially its requirements that (*1*) the T-65 dose be calculable (for two cases, otherwise eligible, it was not), (*2*) the subject be in the ABCC Master Sample defined on the basis of the October 1950 Census, and (*3*) onset be in the interval October 1950- September 1966. For example, Brill et al. (*61*) list several cases in the zone 1.5 - 2.0 km from the Nagasaki hypocenter (air dose about 18 to 120 rads), with onset after 1950, that do not appear in the list of Ishimaru et al., presumably because they were not in the Master Sample. Tomonaga et al. also list six cases exposed at these distances whose date of onset was unknown. In the most recent analysis of death certificate data, Jablon and Kato (*4*) show two deaths in the period October 1950 December 1964 for those with T-65 doses ranging from 10-49 rads, none in the interval 50-99 rads.

The difference between the Hiroshima and Nagasaki data is not only a matter of dose-response and quality of radiation, but also of type of leukemia (Table a-2). Hiroshima and Nagasaki survivors differ markedly in the ratio of acute: chronic types of leukemia (chronic lymphocytic leukemia, rare in Japan, was not associated with radiation exposure in either city). This difference exists despite the diagnostic standardization that has been continually exercised at ABCC under competent hematologic leadership (*12*). In Hiroshima survivors the ratio is 58:30, and in Nagasaki 24:5. If the data of Ishimaru et al. on the type of leukemia are examined in relation to dose, it appears that most of the difference between the two cities lies in the number of chronic cases. For acute cases the curves of incidence are much more similar.

Since a possible cause of the difference in incidence between the two cities is a difference in the quality of radiation, a number of RBE constants have been fitted (*3, 10*) to the total leukemia incidence in the two cities, and an RBE of 5 has been found to give the best fit. However, the authors (*10*) state that "...The Nagasaki curve is quite erratic, betraying the relatively small number of cases upon which it is based, and by the same token, reminds us that we can regard any conclusions that we reach as being, at best, crude approximations to the truth."[1] If the dose in rem[2] at each point is determined by weighting the dose of neutrons by five and the dose of gamma rays by one, the incidence plot can still be represented by a straight line (Figure a-2), and the excess leukemia incidence is approximately 1.7/10^6/year/rem in Hiroshima survivors. There are, then, two estimates obtainable from this report (*3*), on the linear hypothesis, differing by the RBE used for neutrons, for all forms of leukemia combined, for Hiroshima:

RBE = 1	RBE = 5
3.1	1.7

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[1] Lewis, in a personal communication (*12*) points out that a weighted linear regression analysis shows that the leukemia data for Hiroshima and Nagasaki are consistent with a linear model for all values of the RBE from 1.0 to 5.0.

[2] **See footnote 8, page 86 on usage of the term "rem".**

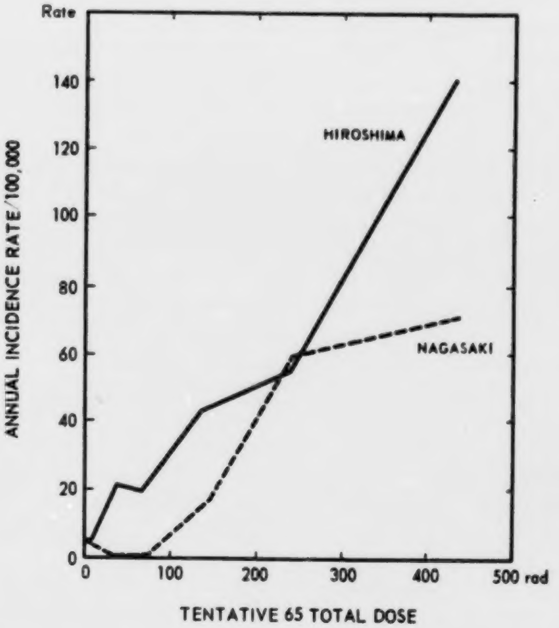

Figure a-1. Annual incidence rate of definite and probable leukemia (all forms) per 100,000 population of A-bomb survivors in the ABCC Master Sample by tentative 65 total dose and city: Oct. 1950-Sept. 1966. (From Ref. 3)

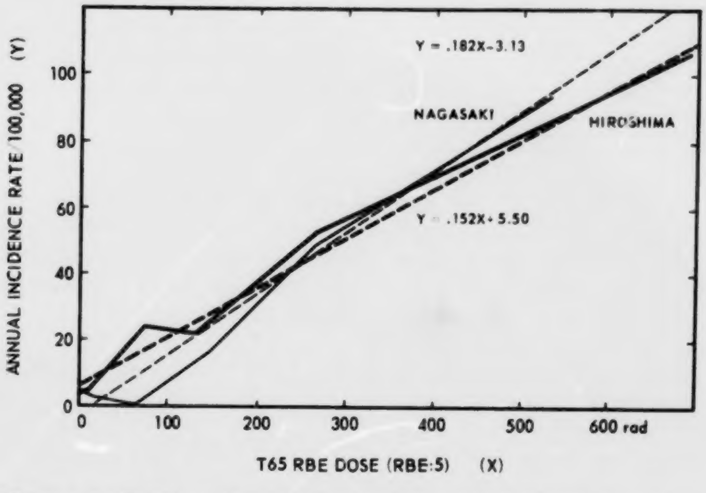

Figure a-2. Definite and probable leukemia in the ABCC Master Sample by T65 RBE dose, 1950-66. (From Ref. 2)

Table a-2

Incidence of Leukemia in A-bomb Survivors by T-65 Dose, City, and Type of Leukemia, 1950-1966, ABCC Master Sample (from Ref. 3)

T-65 total dose (rads)	Person-years at risk	Leukemia cases		Leukemia cases/100,000/yr.	
		Acute	Chronic	Acute	Chronic
		Hiroshima			
300+	12.1	12	5	99.17	41.32
200-299	9.0	2	3	22.22	33.33
100-199	24.1	8	2	33.20	8.30
50-99	38.3	3	4	7.83	10.44
20-49	67.0	6	8	8.96	11.94
5-19	156.0	4	4	2.56	2.56
Under 5	915.1	23	4	2.51	.44
TOTAL	1,222.7	58	30	4.74	2.45
		Nagasaki			
300+	8.4	5	1	59.52	11.90
200-299	10.4	5	1	48.08	9.62
100-199	17.7	3	0	16.95	0
50-99	17.6	0	0	0	0
20-49	20.0	0	0	0	0
5-19	66.3	1	1	1.51	1.51
Under 5	297.2	10	2	3.36	.67
TOTAL	437.6	24	5	5.48	1.14

The excess rate of leukemia for Nagasaki remains about 1.0/10^6/year/rem under either assumption concerning RBE, since neutrons did not contribute significantly to the dose in that city. These estimated excesses can be factored into acute and chronic cases and when this is done (Table a-3) the factors for calculating excess cases/10^6/year/rem become reasonably similar for acute leukemia in the two cities (0.9 and 0.8), but remain appreciably different for chronic leukemia. Additional observations on the Nagasaki survivors are not likely to establish the shape of the dose-response curve in view of the small numbers to be expected.

The estimate of 5 for the RBE of neutrons in inducing leukemia depends heavily on data from the high dose range in Hiroshima. In mammalian radiobiology the shapes of the dose-response curves for neutrons are generally different from those for x rays or gamma-rays, causing the RBE of neutrons to depend on the dose level (or on the magnitude of biological effect). The RBE generally increases with decreasing dose (or effect). From the Hiroshima-Nagasaki comparison, no definite conclusion can be drawn concerning the variation of RBE with dose, although the data are consistent with an increase in the RBE with decreasing dose (*10*). It is considered likely, therefore, that the RBE of neutrons for induction of leukemia at low doses and low dose rates may be higher than the above range of values derived from the Hiroshima and Nagasaki data; however, we emphasize that there were differences between the Hiroshima and Nagasaki experiences other than those of radiation quality, and estimates of the RBE of neutrons derived by comparison of data from the two cities must be regarded as highly tentative.

The published report of Ishimaru et al. includes no information on age at exposure, although the leukemogenic effect is known to be greater in those exposed as children (*3*). In its attempt to provide the scientific basis for practical guidelines for protecting the general population the Subcommittee has preferred to summarize risk estimates with attention to age at exposure, distinguishing exposure *in utero*, during childhood (usually under 10 years of age), and later (usually age 10+). For this reason, and because their report presents data for other forms of cancer in A-bomb survivors through December 1970, the latest mortality data of Jablon et al. (*4*) have been used in preference to the 1950-1966 incidence data of Ishimaru et al. (*3*) in the summary tables at the end of the chapter. Table a-4 provides a summary of the 1950-1970 mortality data for all ages. When the mortality data for 1950-1970 are compared with the incidence data for 1950-1966 it will be seen that (a) the comparable dose-specific rates are lower for the mortality rates, largely because the numbers of leukemia cases change little while the person-years accumulate; (b) the baseline rates are defined differently, those for incidence being based on persons exposed to less than 5 rads and those for mortality on less than 10, and are slightly lower for incidence; (c) the use of the lower dose for calculating baseline incidence yields a lower average dose to which excess cases are referred than is the case in the mortality calculation (54 vs. 72 in Hiroshima, 80 vs. 105 in Nagasaki). In combination these differences reduce the estimates of leukemia deaths/10^6/years/rad below those of Ishimaru et al. The calculations at the level of mortality are shown in Table a-5 and yield estimates of 2.2 for Hiroshima and 0.88 for Nagasaki, vs. the incidence estimates of 3.1 and 1.0 respectively for the shorter period. Table a-5 also provides estimates of excess leukemia mortality by age ATB and by city. Both absolute and relative risks, relative even more than absolute, are higher for those irradiated in childhood.

X-ray Therapy For Ankylosing Spondylitis

The series of British patients treated with spinal irradiation for ankylosing spondylitis (*13, 14*) has been repeatedly analyzed, to yield, on the assumption of linearity in dose response, about one leukemia death per 10^6 persons per year per rad, averaged over a follow-up period ranging up to 25 years. In the latest report (*13*) on this series of 14,554 adult patients treated with therapeutic doses of x rays, ranging (when added over all courses of treatment) from approximately 375 to more than 2,750 rads (mean spinal dose) per patient, deaths from leukemia number 60 observed through 1960, vs. 5.48 expected at British age-, sex-, and time-specific death rates in 141,496 person-years of follow-up. These data are shown in detail in Table a-6. The difference, 46.52 deaths, represents an average annual risk of 329 per 10^6 person-years of observation. If the average

Table a-3

Approximate Factors for Estimating Excess Cases of Leukemia, Based on the Experience of the A-bomb Survivors, 1950-1966 (From Ref. 3)

City of exposure	Total	Acute	Chronic
	(excess cases leukemia/10^6/year/rem)		
	RBE for neutrons = 1		
Hiroshima	3.1	1.6	1.5
Nagasaki	1.0	0.8	0.2
	RBE for neutrons = 5		
Hiroshima	1.7	0.9	0.8
Nagasaki	1.0	0.8	0.2

Table a-4

Mortality from Leukemia in A-bomb Survivors, by T-65 Dose and by City, 1950-1970, JNIH-ABCC Mortality Sample (Extended) (From Ref. 4)

T-65 Dose							
	Mean			No. of	Thousands of	Leukemia Deaths	
Range	Gamma	Neutron	Total	subjects	person-years	Number	Rate*
				Hiroshima			
200+*	269.3	93.9	363.2	1,460	26.7	27	81.6
100-199	108.5	30.1	138.6	1,677	30.2	10	33.1
50-99	56.9	13.3	70.2	2,665	48.3	7	14.5
10-49	17.6	4.3	21.9	10,707	195.4	17	8.7
1-9	2.9	0.8	3.7	13,787	251.7	34	4.3
0	0	0	0	29,943	543.9		
Unknown	-	-	-	1,670	29.8	5	16.8
TOTAL	-	-	-	61,909	1,126.2	100	8.9
				Nagasaki			
200+*	329.1	5.6	334.7	1,310	24.3	15	61.6
100-199	144.3	1.4	145.7	1,229	23.0	3	13.0
50-99	70.3	0.2	70.5	1,231	22.9	0	0
10-49	21.3	0.0	21.0	3,700	67.6	2	3.0
1-9	4.0	0.0	4.0	6,705	123.0	11	5.2
0	0	0	0	4,699	86.9		
Unknown	-	-	-	1,461	27.0	3	11.1
TOTAL	-	-	-	20,335	374.8	34	9.1

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*The T-65 dose estimates for some survivors are so high as to raise serious questions of error. There are 335 persons (Hiroshima 217 and Nagasaki 138) with T-65 doses estimated at more than 600 rads. For these individuals, 600 rads has been substituted for the calculated dose.

Table a-5

Calculation of Excess Deaths from Leukemia, 1950-1970, by Age ATB and City (From Ref. 4)

		Age ATB				
		Total		0-9	10+	
Factor		H	N	H+N	H	N
Person years x 10^{-3}		300.7	137.9	90.03	243.1	105.5
Base-line rate		4.27	5.24	3.25	4.76	5.04
Leukemia deaths:	obs. (0)	61	20	19	50	12
	Exp. (E)	12.85	7.23	2.93	11.7	5.31
	O-E	48.15	12.77	16.07	38.3	6.69
Mean dose, rads		72	105	69	74	113
Excess deaths/10^6/year/rad		2.2	0.88	2.6	2.1	0.56

Table a-6

Observed and Expected Deaths from Leukemia, 1935-1960 Among 14,554 Patients with Ankylosing Spondylitis Treated by X ray, 1935-1955

Followup	Of observation	Leukemia deaths		
		Observed (0)	Expected (E)	O/E
0-2	35,453	7	1.10	6.4
3-5	40,746	19	1.49	12.8
6-8	31,906	14	1.32	10.6
9-11	19,247	6	0.86	7.0
12-14	9,558	5	0.45	11.1
15-24	4,886	1	0.27	3.7
TOTAL	141,496	52	5.48	9.5

dose to the entire marrow, given a spinal marrow dose ranging from 525 to 894 R (*14*), is estimated (see p. 197) to be 372 rads, an estimate of 0.88 deaths from leukemia/10^6/year/rad to the bone marrow is obtained.

Although the spondylitic series provides one of the largest bodies of data on leukemia in man following x or gamma radiation, certain limitations should be borne in mind. Administered in the therapy for a chronic disease, the irradiation was partial-body and varied in pattern of dose, dose rate, and dose-distribution. The derivation of estimates for equivalent whole-body radiation dose thus involves several assumptions. Of perhaps equal importance is the fact that the *excess* leukemia deaths can presently be estimated only on the assumption that such patients have, apart from their x-ray therapy, the same expectation of leukemia as the general population. The study lacks an intrinsic control consisting of patients with the same disease who did not receive x-ray therapy and whose treatment was otherwise the same. A possible contribution of carcinogenic drugs to the tumor incidence in these patients has been suggested but no specific mechanism put forth.

Other Human Experience

Determination of the possible leukemogenic effect of protracted irradiation was sought in a cooperative study of 36,000 patients in 26 medical centers in the U.S. (*15*), who were treated for hyperthyroidism either by radioiodine-131, which has become the most widely used treatment for this disease, or by surgery. Patients treated by surgery, the major alternative form of treatment, were used as controls, although many of them were treated earlier and hence were followed up longer (average 10.6 years vs. 6.5 years). Mean bone marrow doses from ^{131}I were of the order of 7-15 rads received at a comparatively low dose rate. Comparison of the two treatment groups, in accordance with the design of the survey, failed to detect any leukemogenic effects of ^{131}I at this low dose, either in the total sample or when the comparisons were repeated for follow-up periods of fixed length. However, the observed 39 deaths from leukemia were found to be 1.5 times expectation based on U.S. vital statistics, from which it was concluded that patients with hyperthyroidism have an enhanced risk of leukemia, whether treated surgically or with ^{131}I (*12*). The study did not have the power to detect an increase in acute leukemia of 1-2 cases per 10^6 per rad, independent of underlying risk. Lewis (*16*) has since pointed out that the observed rate of mortality from leukemia in the ^{131}I patients was significantly in excess of that seen in the general U.S. population, especially the rate of mortality from acute leukemia in patients of older ages, whereas the excess in the surgically treated group alone was not statistically significant. Nevertheless, because the excess in the ^{131}I group did not differ significantly from that in the surgery group, the data fail to establish the existence of an excess attributable to the radioiodine treatment *per se*.

No excess in leukemia, or in other cancer, has been documented in populations exposed at dose rates within present occupation exposure limits, but workers exposed in the days before current safety practices have shown an excess in leukemia (*1*). Unfortunately, however, it is not possible to make dose estimates of any real precision for such workers, and the major studies provide no basis for quantitative estimates of the leukemogenic effects of occupational radiation (*17-21*). Two of these studies (*20-21*) are negative but include too few person-years of follow-up to exclude the existence of leukemogenenic effects of radiation. The best data are those of Seltser and Sartwell (*17*) who compared members of the American Academy of Ophthalmology and Otolaryngology (AAOO) as to incidence of death from leukemia in the period of 1935-1958. Their observations follow, by age at risk, and with expectations based on the experience of the AAOO:

Age	Obs.	Exp.	Ratio
35-49	2	1.9	1.0
50-64	8	1.1	7.3
65-79	9	4.7	1.9
Total	19	7.7	2.5

Although the experience is not large, it is much larger, in terms of leukemia mortality, than the British radiologists' experience reported by Court Brown and Doll (*20*), and this fact, or a difference in dose, may explain the difference in findings.

The Seltser-Sartwell data on U.S. radiologists are also of interest for their possible relevance to the question of a dose-rate effect for x radiation in man. The total dose received by radiologists practicing in the 1935-1958 period of the survey cannot be quantified in any real sense, but Braestrup (*22*) attempted an approximate estimate for the years 1930-1954 in response to Warren's 1956 report on age at death of radiologists vs. other specialists. Averaging highly variable readings on 1933-1937 installations, Braestrup estimated that the radiologist at that time may have received 100 R per year in contrast to about 1 R in 1957, and suggested 2,000 R as a possible life-time (40-year) occupational dose for radiologists dying from 1930-1954. Marinelli (*23*) has recently taken this estimate as equivalent to about 600 rads to the marrow, and derived from the Seltser-Sartwell report on radiologists an estimated absolute risk of 0.4 deaths from leukemia per 10^6 man-year-rads. The lower 90 percent and upper 90 percent confidence limits on this estimate are 0.20 and 0.56, apart from the uncertainties in the dosimetry, and are below the range of most estimates in the table on pp. 117-118. For several reasons, however, Marinelli's estimate provides no upper bound on the probable risk; (a) the Seltser-Sartwell cohorts had not all completed their professional lives; (b) the exposure period (1945-1958) is later than that to which Braestrup had reference; and (c) Braestrup's 1933-1937 estimate of 400 mR/day is four times the NCRP maximum permissible dose in effect from 1934 to 1949. If the NCRP maxima are taken as the average dose year by year from 1935-1958, a mean dose would be more nearly 800 R on a 40-year basis, and appreciably less for the partial life-time actually observed by Seltser and Sartwell. If Marinelli's calculation had been done on the basis of 800 R the observed excess would have been about one death/10^6/year/rad.

Another occupational study is that of Miller and Jablon (*21*), who compared 6,560 World War II Army-trained x-ray technologists with 6,826 pharmacy or medical laboratory technologists as to mortality through 1963, without finding any clear evidence of radiation-induced leukemia over the 18-year period. Failure to observe a significant increase in leukemia mortality in this instance may well reflect the shorter duration of radiation exposure and lower cumulative doses received by the technologists in comparison with the radiologists; also, a two- or three-fold increase in risk could by chance have gone undetected in a survey of this size.

In three independent studies from Denmark (*24*), England and Wales (*25*) and the U.S. (*26*), an association exists between leukemia in adults and exposure to diagnostic x rays. In each study the association is demonstrable for the myeloid forms of leukemia but not for the chronic lymphatic form. The type of leukemia reported is the same as that seen in persons exposed to heavy doses of radiation. In each study the association is most pronounced for exposures to regions of the body containing active marrow in the adult, i.e., the trunk, as opposed to peripheral regions. In the U.S. study the association is reported only for males; none was shown for the smaller number of females. This greater sensitivity of males is also seen among A-bomb survivors, as well as in the natural incidence of the disease. In the U.S. study, which involved 1,414 leukemia cases occurring in three states during the years 1959-1962, Gibson and colleagues (*25*) estimate the relative risks associated with specific numbers of x-ray films. For example, they find that the risk to males of chronic myeloid leukemia following exposure to 11 or more films to the trunk is 2.2 times the risk from exposure to less than 11 such films. The average dose to the total red marrow from such exposures is expected to be less than 0.5 rad per film. These data are consistent, therefore, with the possibility that repeated small doses of radiation given to males may result in a relative risk of leukemia *per rad* which is comparable to that incurred from a single large dose.

Cogent observations come from studies of patients subject to pelvic irradiation. Four such studies concern radiation used to castrate female patients, for relief of certain benign gynecologic conditions (*27-30*); three studies concern radiotherapy for cervical cancer (*31-34*); and one study concerns both uses of irradiation (*26*). The reports of Doll and Smith (*27*) and Alderson and Jackson (*29*), agree in the finding of leukemia excess after radiation castration, which is greatest in the interval five to nine years following irradiation. The study of Brinkley and Haybittle (*28*) is much smaller and finds no cases of leukemia, as compared with an expected number of 0.24 determined from general population incidence data on cancer registration. Waggoner (*35*) found a leukemia excess in patients exposed to radiation for castration, the excess appearing at all intervals five years or more following exposure. Randall et al. (*30*) found an increased overall cancer mortality following radiation for castration, but their data do not give a breakdown of the cancer into leukemia or other specific sites. Thus, four of the studies find a leukemia excess, one study finds a cancer excess but does not investigate leukemia specifically, and one study is too small to identify an excess of the magnitude report by the others. Relative risks of death from leukemia following radiation-induced castration in three of the positive studies are given as 4.58 (*27*), 2.27 (*29*) and 2.32 (*35*). The dose is given in two of these papers (*20, 21*) in terms of dose to the ovary or to some other intrapelvic position as in the range of 300-1500 rads. Two other papers (*18, 26*) report the mean dose to bone marrow, which range from 40 to 300 rads. Randall et al. give the exposure as 1200 milligram hours intracavitary radium or greater.

In contrast to the studies on radiation castration, none of the reported studies on irradiation for cervical cancer (*31-35*) shows a leukemia excess. The mean marrow dose for the patients in these studies is estimated to be between 300 and 1500 rads, or usually well above the range of dose received in radiation castration. Only a small portion (about 15 percent) of the patients given radiotherapy for carcinoma of the cervix received intracavitary radium alone, in some of whom the radiation dose was in the same range as that received by patients given radiation for castration. The great majority of the cervical cancer patients received external radiotherapy, alone or in addition to intracavitary radium. The finding of no leukemia excess at the higher doses associated with radiotherapy for cancer is not adequately explained. It is conceivable that some sufficiently high dose of radiation is lethal to a high proportion of leukocyte stem cells and that this lethal effect outweighs any leukemogenic effect at these doses (*36*). No model has been presented, however, to describe these two effects quantitatively in the patients of these series. It is also conceivable that the risk of leukemia decreases disproportionately with diminution in the fraction of marrow that is irradiated, as has been observed to be the case in the induction of certain lymphoid leukemias of the mouse (*37*), such that when the irradiated fraction falls below a certain "critical" level (as might be true in patients irradiated for cervical cancer) the risk per rem becomes drastically smaller, if not negligible. Again, however, the existing human data are insufficient to resolve this issue.

An excess of leukemia has been observed in each of three series (*38-40*) of patients investigated after being injected for diagnostic purposes with thorotrast, a colloidal suspension of thorium dioxide. In these series, which together included more than 2,000 patients, the leukemias appeared after an average of 17 years following injection of the radioactive colloid, during which time the marrow was irradiated continually with alpha particles emitted by the thorium, at a rate estimated to average 8-13 rads per year mean tissue dose. Interpretation of this dose in terms of a dose-effect relationship is greatly complicated, however, by nonuniformity in the spatial distribution of the dose within the marrow, the radiation tending to be concentrated in microscopic "hot spots", and by the high LET of the alpha radiations responsible for the dose.

In view of the greater sensitivity of children to the leukemogenic effect of radiation, the follow-up studies of children treated by x ray for thymic enlargement and for tinea capitis are of special interest despite their small size. Among the 1,451 subjects irradiated as infants for thymic enlargement, with an average follow-up of 18 years, Hemplemann et al. found six cases of leukemia in comparison with 0.96 expected on the basis of upstate New York incidence, a relative risk of 6.2 which translates into an absolute risk of $3.0/10^6$/year/rem when the mean marrow dose of 65 rads is taken into account (*41*). A similar estimate is derived from the report of Albert and Omran on 2,043 children treated by x ray (30 rads estimated marrow dose) for tinea capitis and observed for an average of about 15 years (*42*). They found four cases *vs.* 0.9 expected, from which the absolute risk has been estimated at $3.4/10^6$/year/rem.

Other human series have been investigated for evidence of a possible relationship between leukemia incidence and radiation exposure, the results of which have been reviewed elsewhere

(*1*). These include groups exposed medically to radiation from internal and external sources other than those mentioned above, as well as groups residing at different environmental background radiation levels. The studies are insufficient themselves to establish a dose-effect relationship. Hence, the evidence from such studies is not reviewed again in this report.

Radiobiological Considerations Pertaining to Temporal and Spatial Distribution of Dose.

From experiments with animals it may be inferred that the leukemogenic effect of ionizing radiation varies with the quality of radiation, LET, dose rate, total accumulated dose, and perhaps other physical factors as well (*37*). The induction of myelocytic leukemia in mice has been studied following exposure to both gamma rays and neutrons (*43*), and the results are shown in Figure a-3. Although there was no dose-rate dependence with neutron exposure, a striking dependence was seen with gamma radiation, the effect of a single dose being perhaps five or more times that of the same total dose accumulated through daily exposures. The lack of dose-rate dependence for neutrons (*45*) counters the argument (*46*) that the dose-rate effect seen with gamma rays was only apparent and resulted from a difference in age-sensitivity to leukemia induction. Even if that argument were correct, the fact remains that a given dose of gamma radiation delivered at low dose rates over a sizeable part of an animals' life span yielded fewer leukemias than did the same dose delivered in a single brief exposure at an early age, as has been observed repeatedly (*37*).

The dose-rate dependence in leukemogenic effectiveness of gamma rays and the contrasting lack of dose rate dependence in leukemogenic effectiveness of fast neutrons typify the influence of dose rate on the effectiveness of low-LET and high-LET radiations as observed for most effects in mammalian radiobiology (*43*). In general, the reduced effectiveness of low-LET radiations at low dose rates is attributed to repair of incipient stages of injury at low dose levels, associated with which there is usually a corresponding departure of the dose-effect curve from linearity even at high dose rates (Fig. 1, p. 98 curve "b"); in contrast to this situation, the curves for high-LET radiations are typically relatively insensitive to dose rate and are linear (Fig. 1, p. 98 curve "a") (*43*). The induction of neoplasia by radiation may well involve direct injury to individual cells or groups of cells, and possibly to the genetic apparatus of such cells. A definite dose-rate dependence of effect has been seen with respect to genetic effects in the mouse. The data have bearing on a possible dose-rate effect for leukemogenesis in man only if the assumption is made that a "somatic mutation" represents the underlying mechanism.

The data from Hiroshima (large neutron dose component) are consistent with linearity; the Nagasaki curve (essentially no neutron component) suggests curvilinearity with increasing slope as the dose increases. However, because of the small number of cases involved, particularly in the Nagasaki data, it is not possible to conclude that the curves are in fact different. Nevertheless, the apparent differences in the curves do correspond to what has been observed widely in radiobiology, both in tissue culture and for late effects such as leukemia induction (*31, 32*) and lens opacification in the mouse (*47, 48*). Because of the different shapes of the curves for high and low-LET radiation, the RBE increases with decreasing dose. Furthermore, there is generally a differential dose-rate dependence, with little or no dose-rate dependence observed following exposure with high-LET radiation and a definite dose-rate dependence following exposure to low-LET radiation.

In summary there are no data on the human being that allow one to conclude that a dose-rate effect is or is not operative in radiation-induced leukemia in man. A dose-rate effect has been demonstrated for the induction of myelocytic leukemia in the mouse following exposure to low-LET radiation. Radiobiological considerations are cited which are consistent with the dose-rate effect seen in the mouse.

Mechanisms of Leukemogenesis

The pathogenesis of leukemia, like that of other forms of cancer, remains largely unknown. The differences in age distribution of the various forms of the disease in non-irradiated populations (*49-50*) and the absence of

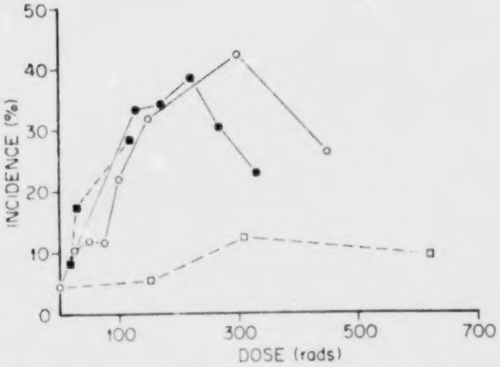

Figure a-3. Myeloid leukemia in male mice. ○ single exposure; □ daily exposures. (Open symbols denote results with gamma rays and x rays; solid symbols, neutrons.) (from Ref. 14) an increase of the chronic lymphocytic form in irradiated populations imply that pathogenetic mechanisms may vary appreciably from one form of leukemia to another.

The presence of the Philadelphia chromosome in the great majority of patients with chronic granulocytic leukemia and the high susceptibility of leukemia associated with congenitial diseases involving chromosomal abnormalities (e.g., Down's syndrome, Bloom's syndrome, and Fanconi's syndrome) suggest that the leukemogenic effects of radiation may possibly be related to radiation -induced chromosomal or genetic damage (*51*). Studies on experimental animals have also implicated leukemogenic viruses, at least in the induction of certain forms of leukemia in irradiated mice (*37*).

The experimental induction of leukemias of diverse types has been studied extensively in irradiated mice and, to a lesser extent, in irradiated rats, guinea pigs, dogs, and monkeys (*37*). At dose rates less than 0.01 rad/min., beagles (*52*), swine (*53*), and mice (*54*) have shown significant increases in the rate of leukemia. Furthermore, reduction of the dose rate below this level by a factor of 3 in the beagles and by a factor of approximately 10 in the swine, failed to abolish the significant increase in the frequency of leukemia and related diseases. In general, the observations in these species are insufficient to establish dose-effect relationships at low dose levels, or to characterize the process of leukemogenesis in detail. Hence, for purposes of estimating risks in human populations, reliance cannot be placed on knowledge of mechanisms but must be placed chiefly on empirical observations derived from study of the occurrence of leukemia in man himself.

Summary of Empirically Determined Risks for Man

Both absolute and relative risk estimates obtained from the major reports cited above are summarized in Table a-7 to provide a basis for arriving at a "best" current estimate for administrative and scientific purposes. This is the first of the summary tables of standard format more fully described in Appendix VI. Only studies generating information directly useful in quantifying risk have been included. The table lists, first, estimates for individuals exposed at age 10 or more; next those exposed as children; and finally, those exposed *in utero*. The *in utero* are shown here merely for comparison; they are discussed specifically in Appendix IIA 2. In addition to the standard definitions and explanations given in Appendix VI, there are special footnotes to Table a-7 relating to specific studies.

For each study listed, Table a-7 gives information on conditions of radiation exposure (type of radiation, duration of exposure, range of external dose, mean tissue dose), size of experience, demographic character of subjects, source of baseline (control) observations, and measures of risk. The risk estimates are of three forms:

1. *Relative risk (col. 16)* - For subjects exposed to a given (mean) dose, the ratio of the observed number of leukemia cases (or deaths) to the expected number.
2. *Percentage increase in relative risk per rem (col. 18)*
3. ***Absolute risk (cols 19-20)*** — The leukemogenic effect is expressed in terms of the excess number of cases (or deaths) per million person-years of observation per rem.

Appendix VI should be consulted for more specific definitions and methods of calculation.

In view of the fact that the estimates for A-bomb survivors pertain to external dose, for which no adjustment to marrow dose has seemed possible, the tabulated studies on individuals exposed as adults are in good general agreement, as are those on subjects exposed as children. The various measures of risk may be summarized as follows:

	Adults	**Children**
Percent increase in relative risk/rem	2 to 3	5 to 10
Absolute risk (cases/ 10^6/year/rad)	1 to 2	2 to 3

These estimates are intended to apply to large population groups; particular subgroups may be at higher, or lower, risk than these average values.

Table a-7

Risk Estimates for Leukemia*

Study population	Reference	Type of radiation	Duration of radiation exposure	Duration of follow-up (years)		Period after irrad. on which risk estimates are based (years)	Number of subjects	Number of person-years	Dose (rads)		Age at irradiation (years)		Sex	Nature of control	Relative risk (O/E)	RBE	Percent increase in relative risk per rem	Absolute risk, deaths or cases/ 10^6/year/rem			Footnotes or other comments
				Range	Mean				Range, External	Mean, to tissue	Range	Mean						Best	Limits Lower 90%	Limits Higher 90%	
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)	(13)	(14)	(15)	(16)	(17)	(18)	(19)	(20)		(21)
Exposed at Age 10 or Older																					
A-bomb H + N 1945	4	$\gamma + n$	< 10"	25	25	6th - 25th	19,472	348,552	10 - 600	86	10+	35	M & F	0-9 rads	$\frac{62}{16.8} = 3.7$	1	3.1	1.5	1.2	1.8	
																5	2.0	.97	.76	1.2	RBE for n taken as 5, γ as 1
A-bomb H 1945	4	$\gamma + n$	< 10"	25	25	6th - 25th	13,630	243,051	10 - 600	74	10+	36	M & F	0-9 rads	$\frac{50}{11.7} = 4.3$	1	4.4	2.1	1.6	2.6	
																5	2.3	1.1	.86	1.3	RBE for n taken as 5, γ as 1
A-bomb N 1945	4	$\gamma + n$	< 10"	25	25	6th - 25th	5,842	105,501	10 - 600	113	10+	31	M & F	0-9 rads	$\frac{12}{5.3} = 2.3$	1	1.1	.56	.09	.98	
																5	1.1	.54	.09	.94	RBE for n taken as 5, γ as 1
Spondylitis Patients 1935-54	14	X	days to years	1-20	5.5	1-20	11,287	61,902	250-2,750	372	15-55+	36	M	England & Wales	$\frac{32}{2.64} = 12.1$	1	2.9	1.3	1.0	1.7	Morbidity
"	13	X	"	5-25	9.7	0-25	14,554	141,796	"	"	"	36	M & F	"	$\frac{52}{5.48} = 9.5$	1	2.3	.88	.71	1.1	Mortality; 84% male
Menorrhagia Patients 1940-60	29	X	min. to mos.	3 - 24	13.6	0-24	2,068	28,125	550-1,050	136	20-55+	46	F	Scotland	$\frac{6}{1.3} = 4.6$	1	2.7	1.2	0.5	2.4	Authors estimated dose to red marrow

*This table does not provide a complete compendium of all studies; see text for selection. See Appendix VI for definitions and methods of calculation. Note that mean dose for A-bomb survivors is *not* a marrow dose, but is always an external dose; others are to the total marrow.

Table a-7 (Continued)
Risk Estimates for Leukemia

Study population	Reference	Type of radiation	Duration of radiation exposure	Duration of follow-up (years)		Period after irrad. on which risk estimates are based (years)	Number of subjects	Number of person-years	Dose (rads)		Age at irradiation (years)		Sex	Nature of control	Relative risk (O/E)	RBE	Percent increase in relative risk per rem	Absolute risk, deaths or cases/ 10^6/year/rem			Footnotes or other comments
				Range	Mean				Range, External	Mean, to tissue	Range	Mean						Best	Limits		
																			Lower 90%	Higher 90%	
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)	(13)	(14)	(15)	(16)	(17)	(18)	(19)	(20)		(21)
Exposed Under 10 Years of Age																					
A-bomb H + N 1945	4	γ + n	< 10"	25	25	6th - 24th	4,507	90,031	10-600	69	0-9	5	M & F	0-9 rads	$\frac{19}{2.93}$ = 6.5	1	8.0	2.6	1.8	3.3	
																5	5.1	1.6	1.1	2.1	RBE for n taken as 5, γ as 1
Thymus X-ray 1926-1957	41	X	mos.	2-35	18	0-35	1,451	26,118	< 61 - 600+	65	0.5	0.5	M & F	Upstate N. Y. Incidence	$\frac{6}{0.96}$ = 6.2	1	8.1	3,0	1.3	5.6	Morbidity. See footnote (b)
Tinea capitis patients 1940-49	42	X	min.	3-22	15	0-22	2,043	30,645	200-400	30	3-12	?	M & F	U.S. Incidence	$\frac{4}{0.9}$ = 4.4	1	11	3.4	0.9	7.7	Morbidity. See footnote (c)

[a] This table does not provide a complete compendium of all studies; see text for selection. See Appendix VI for definitions and methods of calculation. Note that mean dose for A-bomb survivors is not a marrow dose, but is always an external dose; others are to the total marrow.

[b] Only Hemplemann's "series I", those with the heaviest x-ray exposure, is used here. Among 2,073 untreated siblings there were no cases of leukemia compared to 1.48 expected at upstate New York State incidence rates. Dose to marrow is approximate (error may be a factor of 1.5 either way) and is based on an estimate by Marinelli (23) that marrow dose would be 20 percent of the air dose to the thymus.

[c] Mean dose is based on the authors' estimate that 10 percent of the red marrow was irradiated during the scalp treatment for tinea capitis. Expected deaths are not given by the authors and are based on New York State (exclusive of New York City) incidence data (5[illegible] Eighty-six percent were males. 26 non-whites. Among 1,413 non-irradiated tinea capitis patients matched for age, race, and sex, there were no cases of leukemia.

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b. Radiation-induced Thyroid Cancer

Although the thyroid gland is comparatively resistant to destruction by radiation, studies in man and animals during the past decade have demonstrated it to be relatively susceptible to the induction of neoplastic lesions (*1*). The radiation doses associated with the observed neoplastic changes, although lower for x rays than for ^{131}I beta rays in rats (*2*), appear to be of the same order of magnitude in man and several species of experimental animals (*3*). It should be pointed out that in the case of the human population the radiation exposure, although considered to be partial body, involved the entire thyroid gland.

Dose Response

For external x radiation, there are reasonably good dose-incidence data for thyroid neoplasms in man (*4, 5, 10*) and in rats (*6, 7*). The shape of the dose-response curve has not been clearly defined, but with moderately high doses (over 1000 rads) the induction of neoplasms (mainly benign) approaches 100 percent in persons exposed during childhood (Fig. 6-1) (*4, 8*). One study of clinically palpable nodules in three groups of persons irradiated in childhood suggests a linear response (perhaps curvilinear at the higher dose range), with linearity down to relatively low doses (above 20 rads) (*5*) (Fig. b-2). Also, in the Japanese who were under 20 years of age when exposed to the atom bomb explosions, a distinct dose incidence correlation has been reported (*9, 10*).

Dose Rate

There is no good information about dose rate effects for human thyroid cells; however, on the basis of the physical dose absorbed in the

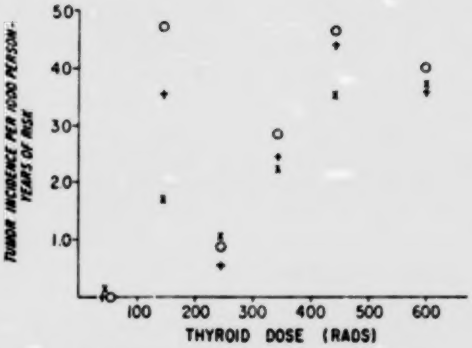

Figure b-1—Incidence of thyroid neoplasms versus thyroid dose (rads): O refers to tumor incidence in the AP-treated individuals of the oldest cohort (born before 1940), + refers to all persons in oldest cohort, and X to those in the two oldest cohorts combined (born before 1950) (Ref. 4).

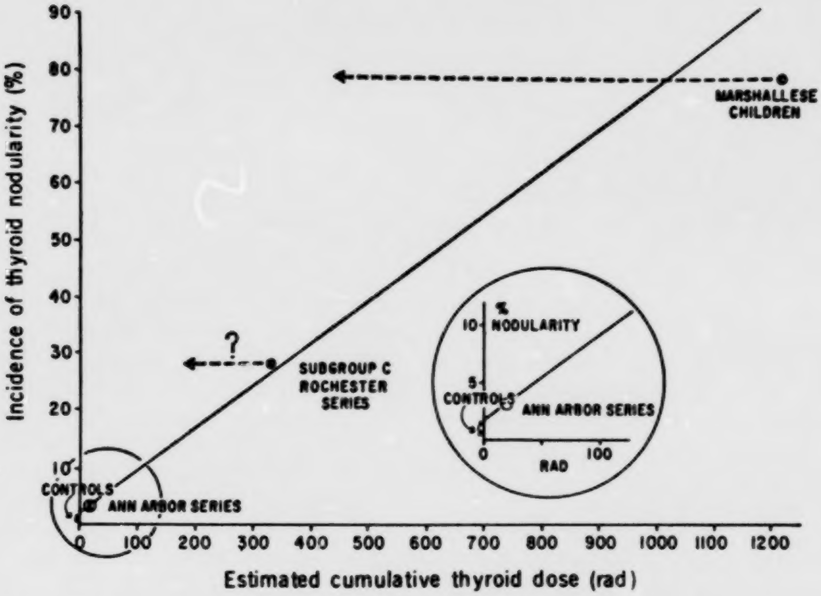

Figure b-2. Incidence of thyroid modularity in relation to estimated cumulative dose to the thyroid gland. The points represent values based on real (or assumed) incidence of nodularity and estimated mean cumulative physical doses to the thyroid gland. The horizontal dashed line and arrow represent the direction in which the mean dose of the Marshallese should be adjusted to take into account the fact that beta-rays from Iodine-131 are probably less effective than x-rays in inducing thyroid neoplasms. Animal experiments indicate that beta radiation is one-tenth to one-fifteenth as effective as x irradiation (*13*); this obviously could not be the case here (unless the estimated dose is too small), because a correction of this magnitude would reduce the dose to the Marshallese thyroids to less than that of the Subgroup C children. The horizontal dashed line and arrow for Subgroup C takes into consideration the possibility that the fractionated doses might be less effective than single exposures—a presumption not substantiated by the evidence at hand (Ref. 5).

gland, there is some circumstantial evidence that beta rays from a mixture of internally deposited radioiodine isotopes are as effective as x rays in initiating tumor formation in children (*5*). The observations in the Marshallese irradiated as children primarily with iodine isotopes from an H-bomb explosion in 1954 are also consistent with those noted after x ray exposure (*8*), although the number of cases is small (one case of thyroid cancer has been found). In this instance, however, the shorter-lived radioiodine isotopes, which are 10 to 20 times more biologically effective than ^{131}I (*11*), were responsible for much of the tissue damage. Hence, the dose rate was not as much lower than that associated with x ray exposures as it would have been if ^{131}I had been the only source of radiation.*

In the cooperative thyrotoxicosis study of patients treated with large doses of ^{131}I, no clear-cut increase in the number of cases of thyroid cancer was noted above that found in hyperthyroid patients not given ^{131}I (*12*). Although the failure of radiation to induce cancer in these patients might conceivably have resulted from resistance of their hyperactive thyroid cells to malignant transformation (*13*), it seems more likely to have been due to the possibility that their doses were in excess of an optimal dose for tumor induction, since their thyroids received many thousands of rads. The presumed explanation for a decrease in the oncogenicity of radiation at high levels, which has been observed in animals as well as in man, is that the radiation damage to thyroid cells at these levels is so severe as to kill the cells or render them incapable of sustained proliferation. Recent evidence has shown upwards of a 50 percent incidence of hypothyroidism five to ten years after treatment of hyperthyroidism with ^{131}I, suggesting that the relevant doses of radiation are in fact sufficient to cause extensive death of thyroid cells (*22*).

Studies of direct chromosomal damage in man have shown that pre-operative tracer doses of ^{131}I which delivered 50-100 rads to the thyroid produced no increase in chromosome aberrations demonstrable in cells cultured from thyroid tissue excised surgically soon after irradiation (*14*, *21*). This is in contrast to the large increase in aberrations (up to 33%) noted in cells cultured from patients who had received 400-780 rads of x rays to the thyroid gland in infancy 31-37 years previously (*14*).

In rats, the carcinogenic effectiveness of ^{131}I, per rad absorbed dose, is approximately one-tenth of that of x rays (*2*). Studies show that ^{131}I is also about one-tenth as efficient in killing thyroid cells in rats as in the same dose of x rays (*15*). Similar but less well quantitated experiments in sheep also indicate that ^{131}I is much less effective in cell killing than is x irradiation (*16*). In producing chromosome aberrations in the hamster thyroid, on the other hand, ^{131}I has been reported to be as efficient per rad as x rays (*17*, *18*). In evaluating such observations for their implications concerning dose rate, one must remember that the radiations from ^{131}I and from x rays differ in energy distribution within the gland as well as in dose rate.

Host Factors

Little is known of the influence of host factors in man; however, the action of thyroid stimulating hormone (TSH) is required for induction of thyroid cancer in animals after carcinogenic stimuli, including radiation exposure (*19*). Furthermore, after irradiation, increasing amounts of TSH are associated with increasing cancer incidence. Cell proliferation kinetics (rapid during adolescence, slower during childhood, and almost static during adulthood) possibly explain the fact that the thyroid cells seem to be more sensitive to the carcinogenic action of radiation in human beings exposed as juveniles than in those exposed as adults (*4*, *9*).

The well-differentiated forms of thyroid cancer tend to run a relatively benign course in young adulthood and middle age, as is perhaps reflected also by the high incidence of benign appearing "occult" thyroid cancers observed at autopsy in the Japanese (*20*). In older age groups, "spontaneous" thyroid cancers have a more malignant course, but whether this is also the case with radiation-induced malignancies in these age groups is not known.

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*Approximately seven-eighths of the total dose due to radioiodine came from decay of ^{131}I and ^{135}I, which irradiated the gland at initial dose rates of 0.28 and 0.6 rads per minute, respectively.

Mechanisms

In animals and in human beings, there is evidence that the pathogenesis of thyroid cancer is a multistage process, involving a primary event causing lasting damage (possibly chromosomal) to thyroid cells, followed by secondary events which promote cell division, thereby allowing the neoplastic potential of the altered cells to be expressed (*19*). Visible damage to chromosomes (aberrations) has been demonstrated in a substantial proportion of cultured cells from irradiated thyroid glands in humans (*14, 21*) and Chinese hamsters (*17, 18*); in one of the human cases, exposure to x rays had occurred 45 years before (*21*).

Of the secondary factors which promote expression of the malignant potential of damaged, yet viable, thyroid cells, stimulation of proliferation by thyroid-stimulating hormone (TSH) is clearly important. In rats, the neoplastic process after thyroid irradiation progresses through a spectrum of stages beginning with cellular hyperplasia, followed by benign neoplasia, and ultimately by malignant transformation (*19*).

Risk Estimates

On the assumption of linearity in dose response, even in the low dose range, the risk of thyroid cancer appearing in adolescence or young adulthood (from birth to 25-30 years) after irradiation in childhood may be estimated (Table b-1) to be of the order of 1.6 to 9.3 cases per year per million children exposed per rem (*4, 5, 10, 22, 23*). Since the time of development of the radiation-induced tumors is age-dependent, the actual risk of tumor induction during childhood is lower than this, and during adolescence it is higher. There is a suggestion that cancer induction may decline as the irradiated population enters the third decade, implying a decrease in risk at later ages (*4*).

In the Japanese A-bomb survivors, the relative risk at high dose levels is not clearly increased for persons 20 years of age or older at the time of exposure, but is definitely increased for those under 20 at exposure (*9, 10*). Another study of subjects treated as adults (age >20 years) for an average of 22 years previously who had received an average dose of 2100 rads of external x radiation showed no cases of thyroid cancer (*24*), although if the absolute risk of cancer induction were 2 cases/rad/year per 10^6 subjects, 20 cases would have been expected. These studies confirm the lesser susceptibility of the adult thyroid to radiation-induced carcinogenesis, as compared with the thyroid of the infant or child.

It should be emphasized that the values given apply only to exposure at high dose rates. Little is known about the risk of tumor induction at low dose rates (< 0.1 rad/hour).

Several studies have not been utilized in making the risk estimates tabulated, for a variety of reasons. Some of the studies, which appeared to show an association between radiation and an increased cancer incidence, have not been used because they did not lend themselves well to quantitative treatment. Other studies did not show such an association and could not be used to estimate a risk other than zero. All reports should, of course, be consulted for a proper understanding of the complexity of the problem of estimating the risks in question.

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Table b-1 Basis of Risk Estimates For Thyroid Cancer, Childhood Exposure*

Study population	Reference	Type of radiation	Duration of radiation exposure	Duration of follow-up (years)		Period after irrad. on which risk estimates are based (years)	Number of subjects	Number of person-years	Dose (rads)		Age at irradiation (years)		Sex	Nature of control	Relative risk (O/E)	RBE	Percent increase in relative risk per rem	Absolute risk, deaths or cases/ 10^6/year/rem			Footnotes or other comments
				Range	Mean				Range, External	Mean, to tissue	Range	Mean						Best	Limits Lower 90%	Limits Higher 90%	
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)	(13)	(14)	(15)	(16)	(17)	(18)	(19)	(20)		(21)
Thymus X-ray 1926-57	4	X	min. to weeks	6-37	16	6-37	2,878	33,060	5-1,200	229	0-1.5	0	M & F	Upper N.Y. State Incidence	$\frac{19}{0.14} =$ 136	1	59	2.5	1.8	3.4	Morbidity; see footnote (b)
" (high-risk) 1931-46	4	X	min. to weeks	17-32	24	6-32	233	4,577	80-1,200	329	0-1	0	M & F	Upper N.Y State Incidence	$\frac{14}{0.60}$	1	71	9.3	6.2	13.3	Morbidity; see footnote (b)
A-bomb H + N 1945	10	γ + n	< 10"	24	24	10th to 24th	811	12,069	10-600	143	0-9	5	M & F	0-9 rads	$\frac{6}{1.60} =$	1	1.9	2.6	.14	4.1	Morbidity
															3.75	5	1.2	1.6	.09	2.6	RBE for n taken as 5, gamma as 1.

[a] This table does not provide a complete compendium of all studies; see text for selection. See Appendix VI for definitions of headings.

[b] The incidence figures (obtained by mail survey) refer to surgically excised thyroid cancers, the histological diagnosis of which has been verified and in most cases reviewed by the authors. An attempt was made to estimate thyroid doses but estimates were undoubtedly in error in many cases.

*This table does not represent a complete compendium of all studies. See text for discussion of studies omitted. The various readings are defined on pp. 195-199.

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c. Radiation-Induced Bone Cancer

Bone cancer is a relatively rare form of cancer in man, and environmental factors which contribute to production of bone cancer are not well known. The first environmental factor identified was radioactivity introduced into workers from exposure to radium dial paint in the early part of the century. Other irradiated groups that have been studied include patients receiving radioactivity or radiation exposure in the therapy of various diseases; e.g., injection of radium isotopes or external x radiation to the skeleton for ankylosing spondylitis or other bone diseases.

Skeletal tumors developing at the site of previous therapeutic external irradiation have been reported in a few dozen instances. The neoplasms, which are of cartilage as well as of bone, include malignant and benign types. The osteosarcomas have arisen after doses generally varying from 3000 rads to more than 15,000 rads, with a latent period averaging about nine years. The ages of affected patients have ranged from less than ten years to more than 60 years (*1*). The benign tumors, which developed after exposure to much smaller doses (usually less than 500 R in air), are chiefly osteochondromas. Among a group of such tumors developing after radiotherapy to the mediastinum in infancy, the interval between irradiation and histologic diagnosis averaged roughly 11 years (*2*). The lower doses associated with the osteochondromas, as compared with the osteosarcomas, imply that susceptibility to induction of bone tumor may be higher in infants than in adults, and that the skeletal tumors induced by irradiation in infancy tend to be predominantly benign, whereas those induced by irradiation in adult life tend to be predominantly malignant (*3*).

Relation of Cancer Rate to Radiation Exposure

Except for the cases of bone cancer associated with x ray therapy, most cases have been associated with deposition of radionuclides in the skeleton. Recent data from the study of Hiroshima and Nagasaki survivors indicate that some bone cancers are beginning to appear in the highest dose group, but the cases are too few for analysis.

Spondylitis patients given x ray therapy to the spine represent a group of approximately 14,000 individuals, 84% males, in whom four cases of bone cancer have been observed, whereas only 0.63 case was expected (*4*, *5*). One cancer case also received ^{224}Ra therapy (*11*). This is the largest group in which quantitative risk estimates can be derived, and it has the further advantage that marked local variations in the dose to bone cells is not a major problem, as it is for internally deposited radionuclides. The follow-up period has been short, however, and the number of observed cases, four, is small; in addition, these patients already had a disorder of musculoskeletal tissues at the time of irradiation. For these reasons interpretation of the findings in relation to estimation of the risk to the general population is difficult.

Another important group of subjects in which the relationship between cancer incidence and radiation exposure has been investigated includes about 770 exposed individuals, mainly dial painters, observed in studies at M.I.T. (*6*) and Argonne National Laboratory (*7*). These subjects, studied originally in two series, are now being followed as a single group by the Argonne National Laboratory Center for the Study of Human Radiobiology. In this group of individuals, most of whom are still alive, there have been 51 bone sarcomas and 21 carcinomas of the head and paranasal sinuses. Four of the carcinoma cases have occurred in individuals who have also developed bone sarcomas. The dose-response data up to the present have been recently summarized by Rowland and associates (*8, 9*). No sarcomas or carcinomas have been seen below a total accumulated mean bone dose of more than 500 rads, but the incidence rises sharply above this point, particularly in the case of the sarcomas. Rowland and coworkers have suggested that an empirical equation of the type $I = KD^2 \exp (D/D')$ provides the best fit for the sarcoma data, where I is cancer incidence, D is cumulative mean bone dose, and K and D' are constants. The exponential term is introduced to account for an apparent fall in incidence in the highest dose range. At lower values of D, an equation of this type reduces to a proportionality between incidence and the square of the cumulative dose. This particular relationship in effect implies a very small probability of radiation-induced bone cancer at low cumulative doses, with a sharply rising value for the higher ranges, certainly a better fit to the observed incidence rates in this group than a strictly linear fit to the data. It should be noted that the majority of the patients in this rather small series have cumulative radiation doses in the lower ranges.

A group of dial painters in Czechoslovakia, Poland, and Switzerland is currently being studied, after having absorbed strontium-90 and some radium-226 during dial painting within the past few decades (*10*). The estimated doses are only a few rads to the bone in these individuals, however, and the likelihood of much pertinent information on cancer risk being available from them within the next decade or two is slight.

Another major group of subjects includes approximately 900 patients given radium-224 for therapy of bone tuberculosis or ankylosing spondylitis in Germany within the last two decades. The results of a follow-up averaging 20 years have recently been reported by Spiess and Mays (*11*). In this group 53 patients have developed bone sarcomas, with periods from initial injection to the time of appearance of the disease ranging from 4 to 20 years. It is significant that within this group of patients with intravenous radium-224 exposure there have been no carcinomas of the cranial or nasal sinuses. The majority of the bone sarcomas occurred in younger patients, with 35 cases observed in 217 individuals less than 20 years of age at the time radium was injected, and 12 in 708 individuals greater than 20 years of age at injection (6 cases have been omitted because the injected dose is not known).

A plot of the incidence of bone sarcoma versus the accumulated skeletal dose appears to be approximately linear for adult as well as juvenile patients, but again, as in so many instances, the lowest dose range has not shown any sarcoma cases, a circumstance explicable by chance, since the numbers of subjects are small. The lowest cumulative dose at which a bone sarcoma has occurred is 90 rads, and the tumor occurred in one of the adults. According to Spiess and Mays there are at least another 1,000 to 2,000 individuals in Germany who have been given radium-224 therapeutically, and a follow-up study of these patients would be helpful in defining the dose-response curve in the lower ranges. Since this form of treatment of ankylosing spondylitis is still being used in Europe, additional patients may be expected also to become available for study.

With regard to the dosimetry from ingested radium-226, radium-228, radium-224, or other members of the decay chain of the major uranium series, the most detailed treatment of this problem has been given by Marshall in a preliminary report (*13*). In his analysis he attempts to separate the dose to bone surfaces from that delivered to the interior portion of the noncellular calcified bone crystals. For the alpha-emitting radionuclides that are bone seekers, the calculation of the dose to the surface cells is believed to be the most relevant parameter, since these cells are not efficiently irradiated from radioactivity deposited in mineral volume. On the basis of this model, the apparent discrepancy between the results obtained with radium-224 and those with radium-226 and radium-228 is clarified. Spiess and Mays have calculated the effective dose to the bone surface with a model such as has been described by Marshall and Rowland, and according to their calculations the average skeletal dose, which has been given above in relation to the cancer incidence, is not the relevant exposure criterion; it is the dose to cells on the bone surface that is relevant (*11*). When the mean local dose to the soft tissue layer within 10 microns from the bone surface is calculated, they estimate that for radium-224 this local dose is 9 times the average skeletal dose, on the assumption that half the skeletal radium-224 decays on bone surfaces. In contrast, for radium-226 the average soft tissue surface dose is less than the average skeletal dose by a factor of 0.63. On the basis of the surface dose, therefore, the lowest dose at which cancer has been observed in man is approximately the same for the two radioisotopes, 810 rads for radium-224 and 570 rads for radium-226, suggesting the possibility that, based on follow-up periods of at least 20 to 30 years, a threshold could exist for carcinogenesis by radium isotopes. As yet, however, no conclusion on this point can be drawn because of the small population at risk in the lower exposure range. Further study of the radium-224 patients should help resolve this problem. An interesting footnote to the work with ^{224}Ra is that in those patients who received the radium injections for shorter periods of time (i.e., about 3 months), the incidence per rad was one-half as great as in those who received more protracted exposure (*11, 12*).

It is noteworthy that the new dosimetric models, on which the risk ultimately must be based, are both biological and physical in their approach. It has long been recognized that the radiation dose from "hot spots" in bone, that is, from local relatively high concentrations of radioactivity, appears to be less well correlated with biological effects than is the dose from the more diffusely deposited radionuclides. It has been concluded from this fact that the "hot spot" results in "overkilling"; i.e., it generally causes local cell death and thus irradiates acellular portions of the bone, a conclusion which is consistent with the more recent models. In calculating bone dosimetry from internal bone-seeking radionuclides, it seems likely that in the future the relevant dose will be the integrated dose to the cells at bone surfaces, and considerable efforts are now being made to assemble relevant metabolic data as a basis for calculating the integrated dose for all of the radionuclides of interest. For example, Marshall has summarized the information on surface retention for radium-226, using available kinetic data (*13*), and he has shown that the surface retention for radium-226 would be relatively short from a single exposure. On this basis, therefore, the *average* skeletal dose from radium-226 would be expected to include a substantial fraction of wasted radiation, in that the radiation would not be delivered to the cellular elements at the bone surface. The same argument applies also for calcium-45 and americium-241. Plutonium and thorium have been recognized as remaining with the bone surface until resorbed or buried under new bone, and hence they will give higher surface doses per average rad to bone, a conclusion supported by animal studies. Mays (*14*) estimates that "monomeric" plutonium-239 is about 9 times more effective on the basis of average skeletal dose than radium-226, with polymeric plutonium-239 somewhat less effective than the "monomeric" form. This distinction between the forms in which plutonium may reach the bone illustrates the importance of physico-chemical factors in the microdosimetry from these radionuclides.

Host Factors in the Relation to Bone Cancer

One obvious factor which contributes to the probability of bone cancer development in man is age at the time of exposure. For young individuals, and possibly also in those exposed *in utero*, the rapid deposition of bone-seeking radioelements during active bone growth might confer a higher risk of cancer than in adults. It should be noted, however, that long-term exposures to low levels of long-lived radionuclides may not necessarily lead to a higher risk when the exposure begins prior to birth than when exposure begins at a later age, if the dose is accumulated very slowly.

In patients exposed to radium-224, there was no significant difference in the incidence of bone cancer by sex. Since this group of patients also had pre-existing bone disease, Spiess and Mays (*11*) attempted to determine whether their cancers were more likely to appear in the areas of bone affected by the disease, and they concluded that there was no predilection for cancer to develop in regions with active tuberculosis or spondylitis.

Experimental Studies

The body of information which has accumulated from experimental studies in a number of species is greater for the bone-seeking elements than for any other group of internal emitting radionuclides. Many of the experiments evaluate the effects of low doses in long-lived species. Experiments have been summarized recently in a symposium held at Sun Valley, Idaho, in 1967 (*15*), and also by Mays and Lloyd (*16*), and by Mays' (unpublished) report for the NCRP committee. The particular radionuclides whose long-term cancerogenic effects have been investigated are plutonium-239, thorium-228, americium-241, strontium-90, radium-226, radium-228, and calcium-45. One of the principal purposes of these studies has been to compare the relative radiotoxicity of these different radioelements.

The dose-response evidence obtained to date for strontium-90 indicates that as in the case of radium-226 in man there appears to be a lower limit of dose at which no significant cancer effects have yet been observed, and Mole (*17*) has concluded that a relationship $I = KD^2$ is applicable for ^{90}Sr. For plutonium-239 and thorium-228 the evidence indicates a significant probability of cancer induction even at relatively low average skeletal doses (*15*). These experimental studies reinforce the view that alpha-emitting radionuclides are more effective than are beta-emitters, such as strontium-90, and that those radionuclides which tend to be translocated to the interior of bone will show a lower cancer probability for the same total dose to bone than those which remain on the bone surface.

Summary of Human Data and Estimate of Radiation Risk for Bone Cancer

Table C-1 summarizes the data for the three populations in which risk estimates can be calculated. Dose-response curves for the two radium-injected groups are shown in Figs. c-1 and c-2.

The data for the ^{224}Ra-injected patients are consistent with the linear nonthreshold dose-response curve within the limits of the dose range available and when the dose is expressed as mean dose to bone. The data for ^{226}Ra are more consistent with a curvilinear relationship between cancer rate and mean bone dose although a straight line fit to the data cannot be excluded within the statistical confidence limits. This subject has been highly controversial, and it is apparent from the figures that as of now a final determination of the dose-response relationship for ^{226}Ra in bone cannot be made. Until the difference between the two radium groups has been resolved, perhaps by use of a bone cell dose model such as has been developed by Marshall, the risk will be calculated as the average for each entire group.

In the following summary table the correction from rad to rem is made by using an RBE (or QF) of 10 for alpha irradiation.

SUMMARY OF RISK ESTIMATES FOR BONE CANCER

Irradiated as Adults (20 years)

	Absolute Risk Cases/10^6/yr per rem* mean bone dose	Relative Risk % Increase in Rate/year per rem* mean bone dose
^{226}Ra Pts.	0.11	0.71
^{224}Ra Pts.	0.55	5.5
Spondylitics	0.10	1.4

Irradiated as Children (1-20 years)

	Absolute Risk Cases/10^6/yr per rem* mean bone dose	Relative Risk % Increase in Rate year per rem* mean bone dose
^{224}Ra Pts.	0.96	9.6

*Correction to rem on assumption that RBE = 10 for alpha particles

Table c-1

Basis of Risk Estimates for Bone Cancer*

Study population	Reference	Type of radiation	Duration of radiation exposure	Duration of follow-up (years)		Period after irrad. on which risk estimates are based (years)	Number of subjects	Number of person-years	Dose (rads)		Age at irradiation (years)		Sex	Nature of control	Relative risk (O/E)	RBE	Percent increase in relative risk per rem	Absolute risk, deaths or cases/ 10^6/year/rem			Footnotes or other comments
				Range	Mean				Range, External	Mean, to tissue	Range	Mean						Best	Limits		
																			Lower 90%	Higher 90%	
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)	(13)	(14)	(15)	(16)	(17)	(18)	(19)	(20)		(21)
Radium-226 Exposed Group 1915-35	7,8	α	years	36-56	49	11th - 56th	775	26,296	< 1 to 50,000	1,700	13+	45	M & F	United States	$\frac{48}{.39} =$ 122	10	0.71	0.11	0.087-0.13		See footnotes (b), (c), more than 90% F.
Radium-224 Treated Patients 1944-64	10	α	mos. to years	5-25	19	4th - 25th	925	12,115	< 50 to 5,750	441	1-70	C 30	M & F	Germany	$\frac{45}{.12} =$ 372	10	8.4	.84	.68	1.0	Expected deaths based on rate of 10/10^6 P-Y, cited in ref. 10
Radium-224 Treated Patients 1944-54	10	α	mos. to years	15-25	21	4th - 25th	217	3,301	< 50 to 5,750	1,103	1-20	10	M & F	Germany	$\frac{35}{.033} =$ 1061	10	9.6	.96	.76	1.2	" "
Radium Treated Patients 1944-64	10	α	mos. to years	5-25	18	4th - 25th	708	8,814	< 50 to 1,000	204	21-70	40	M & F	Germany	$\frac{10}{.088} =$ 114	10	5.5	.55	.34	.85	" "
Spondylitis Patients 1935-54	3,4	X	days to years	5-27	11	6th - 27th	14,554	89,432	250-2,750	372	15-55+	?	M & F	England & Wales	$\frac{4}{0.63} =$ 6.3	1	1.4	.10	.034	.22	84% male; see footnote (d).

[a] This table does not provide a complete compendium of all studies: see text for selection. See Appendix VI for definitions of headings.

[b] Person-years were calculated on the following assumptions: 100 percent survival to 10 years after beginning exposure with uniform death rate thereafter, and 74 percent survival at cut-off of observation in 1971.

[c] Observed cases do not include three cases of bone sarcoma diagnosed prior to 10 years from first exposure: expected number based on a mean incidence rate in the U.S. of 15 per 10^6 per year, applicable to the period from 1930-1970.

[d] Observed and expected data differ from those published by Court Brown and Doll in 1965 (4). According to a personal communication from Dr. Doll (December 1971), four cases of primary bone cancer in the study group have been verified and thus the correction of expected cases to 1.11 from 0.63, used in 1965 to correct for errors of death certification, need not be applied.

*(See *legend on table b-1, e.g.)

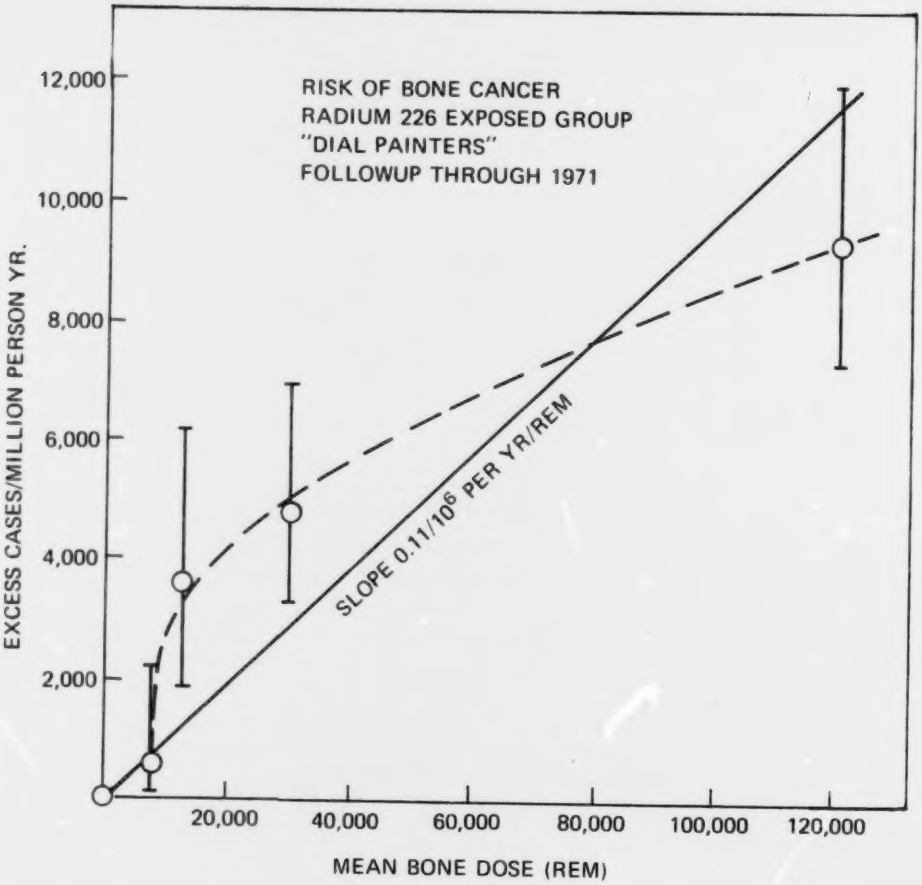

Figure c-1. Dose-response data for bone cancer in Argonne National Laboratory series of subjects exposed to radium-226 in period from 1915 to 1935 (*8, 9*). This group includes dial painters and some patients given radium therapeutically.
Ordinate: Excess bone cancer cases per million person years
Abscissa: Mean bone dose in rem (RBE=10).
The dashed line is drawn by eye through the points; the solid line is the weighted mean slope taken from Table c-1. Error bars based on Poisson statistics and include 90% range (see Appendix IV).

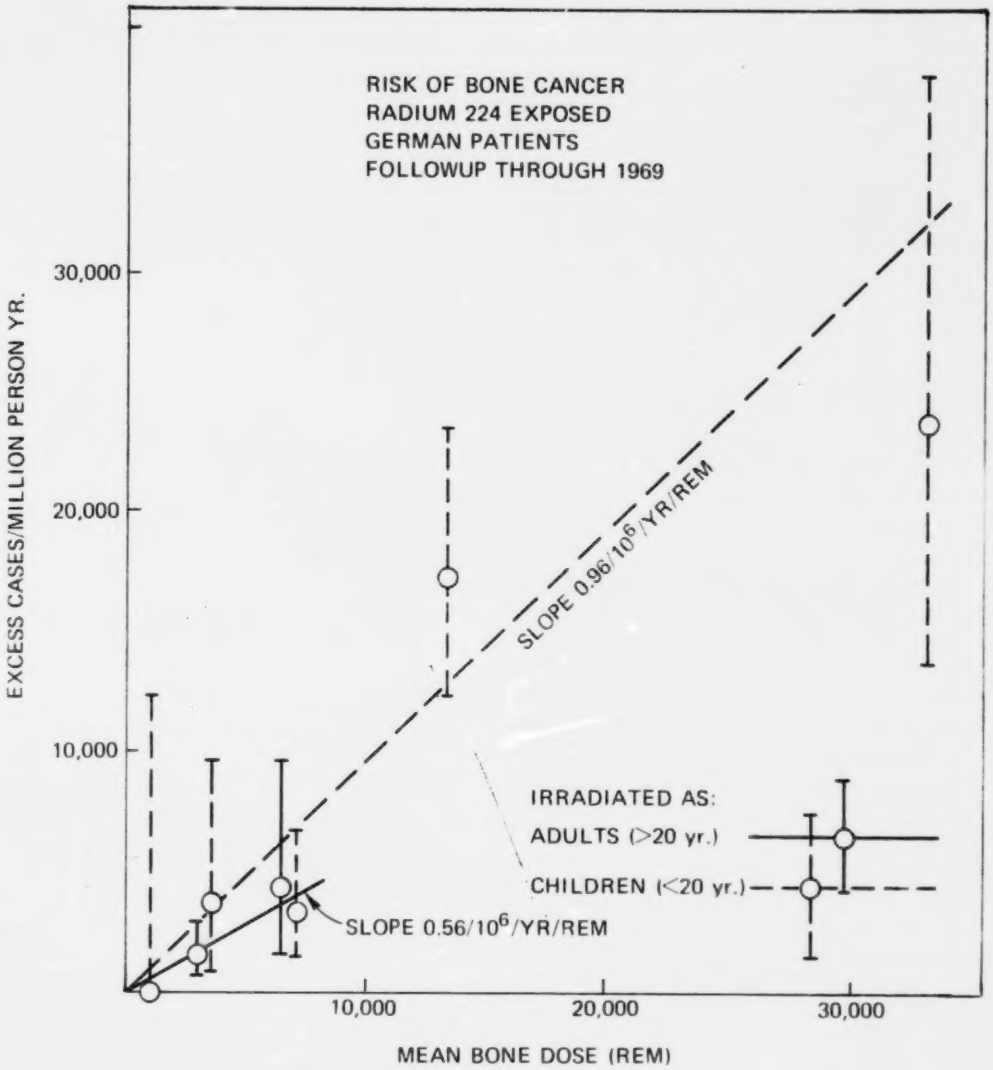

Figure c-2. Dose-response data for bone cancer in German patients given radium-224 therapeutically (*11*).
Ordinate: Excess bone cancer cases per million person years.
Abscissa: Mean bone dose in rem (RBE = 10).
Open circles and dashed error bars: Patients given doses as children (less than 20 years of age); closed circles and solid error bars: Patients given doses as adults (greater than 20 years of age).
Error bars calculated as in previous graph (see Appendix IV).

There is not close agreement among the three studies, particularly the two groups exposed to the radium isotopes. If, however, a quality factor of 7 is applied for radium-226 and a quality factor of 50 is applied for radium-224 (to take into account differences in surface dose as well as in LET), then the relative risks for adults are 1.0, 1.1, and 1.4 percent for the three groups of adults, and 1.9 for the children. The absolute risks would be 0.16, 0.11, and 0.10 for the adults. Such an analysis indicates that the surface alpha irradiation from ^{224}Ra is about 7 times as effective as the alpha radiation from ^{226}Ra, in reasonable agreement with animal experiments and with the analysis of Spiess and Mays cited above.

The risk estimates from the ^{224}Ra-injected patients are probably low because this group is still under study and substantially more cases are likely to appear. On the other hand, the risk estimates in the Argonne series are likely to be too high for low cumulative doses, principally because of the evident non-linearity of the dose-response curve. For the group of x-irradiated spondylitis patients studied by Court Brown and Doll, more cases will probably occur with longer follow-up, but in this instance there is the problem of comparing x-ray data at high dose rates to data from internal alpha irradiation at low dose rates.

It does not appear possible to define the risk of bone cancer with greater precision at this time, but it is worthwhile to emphasize again that each bone-seeking radionuclide will require further evidence on which to base a quality factor in determining the relevant rem dose to the sensitive cells. It is particularly important to obtain such information for plutonium, which is comparable to ^{224}Ra in the distribution of dose to the surface cells. For this purpose, animal experiments may be the only practical way to estimate risks, and we are fortunate that a growing body of relevant experimental data already exists.

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d. Skin

The incidence of cutaneous cancer is increased following intensive irradiation of the skin, especially in the presence of chronic radiodermatitis. The types of neoplasms most commonly reported vary in frequency, depending on site, dose, dose rate, and type of radiation *(1-3)*. Both squamous-cell carcinomas and basal-cell carcinomas have been noted, the latter more commonly on the head and neck. Sarcomas of subcutaneous tissues, which are infrequent, have been found most often in association with long-standing and severe radiodermatitis.

Dose Response

Traenkle (*2*) has suggested that total doses greater than 1000 roentgens (R) are required to produce skin cancer. Sulzberger et al. (*4*), in the only prospective study of the incidence of malignancy in patients receiving superficial radiation therapy for both benign and malignant conditions, found epitheliomata in 6 of 1000 U.S. patients irradiated previously and the same lesion in 9 of 1000 patients who had not been irradiated. They reported no sequelae below 1000 R and only mild chronic changes between 1000 R and 2630 R.

In contrast to the findings of Sulzberger et al. (*4*), Takahashi (*5*) has reported data suggesting that the relative risk of skin cancer in Japanese may be increased by 500-2000 R (Table d-1). In a retrospective statistical study on human cancer induced by radiation they observed 8923 patients with cancer, 207 of whom had skin cancer, as compared with 289 who had malignant lymphomas (skin cancer is relatively rare in Japan). For this entire group of patients, the history of previous radiation was not different from that found in a control group of 11,556 persons. Subsequently, the authors selected 308 cases of skin cancer entering various hospitals. Of these, 14 (4.55%) had received radiotherapy of the primary site (Table 1), whereas only 6 out of 762 (0.79%) in the control group were so exposed. However, Takahashi's finding of a relatively high risk of radiation-induced skin cancer among the Japanese (*5*) stands in contrast to data on the natural incidence of skin cancer, which indicate higher rates in white races than in nonwhite races (*21*). At the same time, a study of A-bomb survivors at Hiroshima reported in 1961 showed no evidence of radiation-induced acceleration of age dependent changes in skin as measured by the appearance, elasticity, and looseness of the skin or by graying of the hair (*14*); moreover, no increase in skin cancer has been reported in atomic bomb survivors (*15*).

Martin et al. (*6*) reported a relative risk of 3.74 in 649 irradiated U. S. patients but were not able to provide dose estimates. The doses were several thousand R or more in the few cases shown.

In 2043 children treated by x-ray epilation for tinea capitis (ringworm of the scalp) Albert et al. (*7*) found 2 cases of basal cell skin cancers, both in white males. Dose estimates ranged between 450 and 850 rad (*8*). No skin cancers were found in 1413 patients with tinea capitis who were not irradiated.

A re-evaluation of this population by R. E. Albert in 1972 (*9*) now reveals 6 basal cell carcinomas in the irradiated group of which 4 are in or on the edge of irradiated areas corresponding to doses of about 450 rad or more. Three of the six irradiated patients have other basal cell tumors not in the irradiated sites and there are 2 basal cell carcinomas in the 1413 controls. The occurrence of 6/2043 cancers is not statistically different from 2/1413 cancers

Ridley (*10*) reports retrospectively 6 cases of basal cell cancer of the scalp in white children aged 5-9. These occurred from 7 to 53 years after treatment at doses of about 475 R.

In the British study of long-term effects of irradiation in patients with ankylosing spondylitis, no deaths were found from skin cancer, even though the skin was included in heavily irradiated sites (*11*). Recently, five British patients who had received 1000-8875 R to the spine and other joints for rheumatoid arthritis were found to have developed multiple basal-cell cancers, and in two other cases there were fibroephitheliomata of Pinkus (*12*). In a brief note, Meara (*13*) noted six similar cases with multiple basal-cell epitheliomata, three of whom also had premalignant fibroepitheliomata. At present, there is no way to determine whether any of these patients were included in the original studies by Court Brown and Doll (*11*).

In rats, the incidence of skin tumors induced by a single exposure to electrons, ranging from 230 to 10,000 rads, has been observed to rise abruptly between 1000 and 2000 rads, reach a peak of about 3000 rads, and fall rapidly with further increase in the dose (*16*). In mice, tumor induction following superficial beta irradiation has been reported to be proportional to the square of the dose (*17*).

Table d-1-Relative Risks for Skin Cancer at Various Exposure Levels After Therapeutic Radiation (External Sources) (*16*) (Computed from data of Takahashi et al (*5*))

Estimated exposures (Roentgen)	Proportion of cancer cases %	Proportion of controls %	Relative risk 95% limits of brackets
0.........	95.45 (294)	99.43 (4,044)	-
500-2,000..........	0.97 (3)	0.25 (10)	4.1 (1.2-9.6)
2,000-4,000..........	0.97 (3)	0.25 (10)	4.1 (1.2-9.6)
4,000-6,000..........	0.65 (2)	0.05 (2)	13.7 (1.8-100.0)
6,000-8,000..........	0.65 (2)	0.02 (1)	27.4 (2.5-300.0)
8,000-10,000.........	0.97 (3)	-	-
10,000.........	0.32 (1)	-	-

Host Factors

The frequency of skin cancers appears to be related to the severity of pre-existing radiodermatitis, in that it is far more common (of the order of 10-28%) in severe cases and relatively uncommon (about 1%) in association with mild changes *(2)*. Occasional cases of skin cancer have been reported in irradiated sites in the absence of clinical evidence of radiodermatitis. Whether these represent coincidental occurrence or an effect of radiation cannot be determined.

The influence of pigmentation, which influences susceptibility to ultraviolet irradiation and hence to naturally occurring skin cancer, is not known.

Mechanisms

The pathogenesis of cutaneous cancer is not fully understood, but clinical and experimental observations imply that gross injury of the skin greatly enhances the process *(20)*. Cancer may thus be viewed as the end result of a series of changes, only some of which are detectable soon after irradiation. These changes, in order of increasing severity, are (1) threshold erythema—a distinct reddening produced by vasodilatation—(2) dry desquamation—loss of superficial layers of epidermis—(3) moist desquamation—exudative reaction with loss of the basal layer of epidermis—and (4) necrosis, from dermal destruction *(18)*.

As long as chronic ulceration is avoided, the skin usually returns to a nearly normal appearance; however, clinically evident and permanent changes occur after doses which produce only dry desquamation. With severe injury to the dermis, the changes also eventually include dermal fibrosis and endarteritis. Since rate and degree of change are affected by many factors (e.g., dose, dose rate, spatial distribution of dose, region of body exposed, total area involved, blood supply, presence of irradiation, and the influence of drugs or other factors), these variables must be taken into account in considering the probability of injury attributable to a given dose *(18, 19)*.

At non-necrotizing dose levels, radiation has been postulated to act as an "initiator" of the cancer process in mice, in a manner analogous to that in which certain carcinogenic chemicals have been observed experimentally to induce cutaneous tumors *(22)*. According to this hypothesis, radiation is conceived to cause permanent changes in cutaneous cells whose subsequent expression is enhanced by promoting factors which in themselves may not be carcinogenic.

In the rat, irreversible radiation injury of hair follicles may be envisioned to act as such a promoting factor, in that the probability of radiation-induced skin tumors has been observed to depend heavily upon it *(12)*. Whether an analogous model is applicable to carcinogenesis in human skin is speculative; however, the association between neoplasia and radiodermatitis tends to argue for the possibility that gross injury of the skin contributes in some way to the evolution of the cancer process.

Risk Estimate

Although evidence suggests that the probability of radiation-induced skin cancer is greatly increased in the presence of radiodermatitis, the data are insufficient to document the induction of skin cancer at doses below the level required to cause radiodermatitis, suggesting that the susceptibility of the skin to radiation carcinogenesis may be lower than that of certain other tissues, such as the thyroid and the bone marrow. The possibility remains, however, that the absence of recorded cases may be attributable to unusually long latency or to under-reporting of skin neoplasms. In the absence of further data, numberical estimates of risks at low dose levels would not seem to be warranted.

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e. Breast

Three different populations of women exposed to ionizing radiation have revealed an incidence of breast cancer in excess of that found in comparable nonirradiated populations. The first of these populations, a series of tuberculous female patients in a Nova Scotia sanatorium, was first reported by the late Ian MacKenzie (*1*). At the time of his report, in 1965, his follow-up included 13 cases of breast cancer in 271 patients subjected to repeated chest fluoroscopy for artificial pneumothorax, as compared with only 1 case which developed in 570 patients who were not fluoroscoped. The study of these patients was later extended by Myrden and Hiltz (*16*), who reported 22 cases of breast cancer in 300 tuberculous women subjected to repeated fluoroscopies, as compared with 4 cases in 483 women not fluoroscoped.

A significant increase in the incidence of breast cancer in female A-bomb survivors was first reported by Wanebo et al. (*2*), from a study of 12,003 women in the Adult Health Study sample. Examinations of these women from 1958 to 1966 revealed 5 definite cases of breast cancer in 5,540 women exposed to less than 9 rads or not in the city at the time of the bomb, as compared with 15 definite cases in 3,762 women exposed to doses larger than 10 rads. A chi-square test on the heavily irradiated women (>90 rads) versus the lightly irradiated women (<90 rads) revealed a significant increase at the 1% level. This elevated risk of developing breast cancer in the A-bomb survivors has now been confirmed in the latest report of mortality in the JNIH-ABCC Life Span Study sample (*13, 18*). However, a significant excess of deaths from breast cancer did not appear until the 1965-70 time period, when 19 deaths occurred in those exposed to doses of 10 rads or more, as compared with an expectation of 4.9 from the rate in the 0-9 rad control group. This 15-20 year minimum latent period is perhaps not surprising in view of the often long history of breast cancer from its detection to its fatal outcome.

Finally, a significantly increased rate of breast cancer has been reported in women given localized x-ray treatments for acute post partum mastitis (*3*). In this series of 606 women, 13 cases were reported, as compared with 5.9 expected from New York State incidence figures. Although the number of cases of cancer attributable to radiation in each of these populations is not large, it is likely that the radiation was the causative agent, and from each study risk estimates can be derived as discussed below.

Corroborative evidence that the *increase* in the number of breast cancers seen in human populations was induced by radiation comes from the demonstration of a carcinogenic effect of radiation on breast tissue in laboratory animals (*4*).

Dose Response

Data on the incidence of breast tumors in irradiated women are too meager to allow a precise evaluation of the dose response. The series with the largest number of cancer cases (and hence the most likely to provide information on the dose-reponse relationship) is the Nova Scotia study, the data from which are shown in Figure e-1. Although these data are consistent with linearity, they cannot be used as evidence for a linear dose-response curve owing to the extremely fractionated nature of the irradiation in this study.

A steep dose-incidence curve has been observed for mammary adenocarcinomas and mammary adenofibromas (either alone or combined) in rats exposed to x rays or ^{60}Co gamma rays (*5,6*), and for the overall incidence of all types of mammary neoplasms in rats exposed to fission neutrons (*7*), as judged one year after exposure. The dose-response curve for the combined incidence of all such tumors (malignant and benign) appears linear down to doses as low as 15 R of gamma rays. In all studies, the response tends to plateau in the high dose range. Although it is clear from these studies that radiation hastens the onset of mammary neoplasms, it is not certain whether there is a corresponding dose-dependent increase in the total number of tumors in rats observed throughout their entire life span, since the natural incidence rises sharply in aged controls.

Mice exposed to whole-body radiation from a nuclear detonation showed an increase in total incidence of mammary carcinomas and sarcomas at intermediate dose levels; however, at higher dose levels, the incidence plateaued and then decreased (*8*). Breast tumor development in irradiated mice is complicated in some, but not all, cases by the presence of radiation-induced ovarian granulosa cell tumors which may stimulate the growth of mammary tumors through the secretion of estrogen (*9*).

Dose Rate

Although there are no good quantitative data concerning the influence of dose rate on induction of breast cancer in women, a comparison of the risk estimates in Table e-1 indicates that extreme fractionation of the total dose makes little or no difference in the absolute risk per rad of developing cancer. For example, the risk estimates from the postpartum mastitis and the fluoroscopy series are indistinguishable, despite the fact that the total dose divided by the total time in the latter series was at least an order of magnitude less than in the former. Perhaps an even more appropriate comparison, that of the A-bomb survivors (to whom the dose was delivered within seconds) with either of the two Western series, indicates that fractionation of the dose does not significantly reduce the absolute risk per rad of developing breast cancer.

Corroboration of this tentative conclusion comes from animal data: in rats, for instance, lowering of the dose rate of x or gamma irradiation causes only minimal reduction of the oncogenicity; a dose rate sparing effect (from 10R/min to 0.03R/min) has been found only for the induction of mammary adenocarcinomas at a total dose of 265 R no dose-rate sparing effect having been found for the mammary fibroadenoma or the total mammary neoplastic response to any dose studied (*10*). Likewise, fractionation of a dose of x rays into successive exposures delivered at a high dose rate has been observed to reduce its tumor-producing effectiveness only slightly (*11*).

Host Factors

Data from the JNIH-ABCC Life Span Study sample for the period 1965-70 reveal a marked decrease in the relative sensitivity of the breast to cancer induction with advancing age at the time of irradiation (*18*). Figure e-2 shows the ratio of breast cancer mortality in survivors exposed to 50+ rads, as compared with that in the 0-9 rad group, in terms of age at the time of the bomb (ATB) and age at death. If this same dependence of relative risk on age at the time of exposure were to hold for Western populations, the age-specific variation would disappear when judged in terms of the absolute

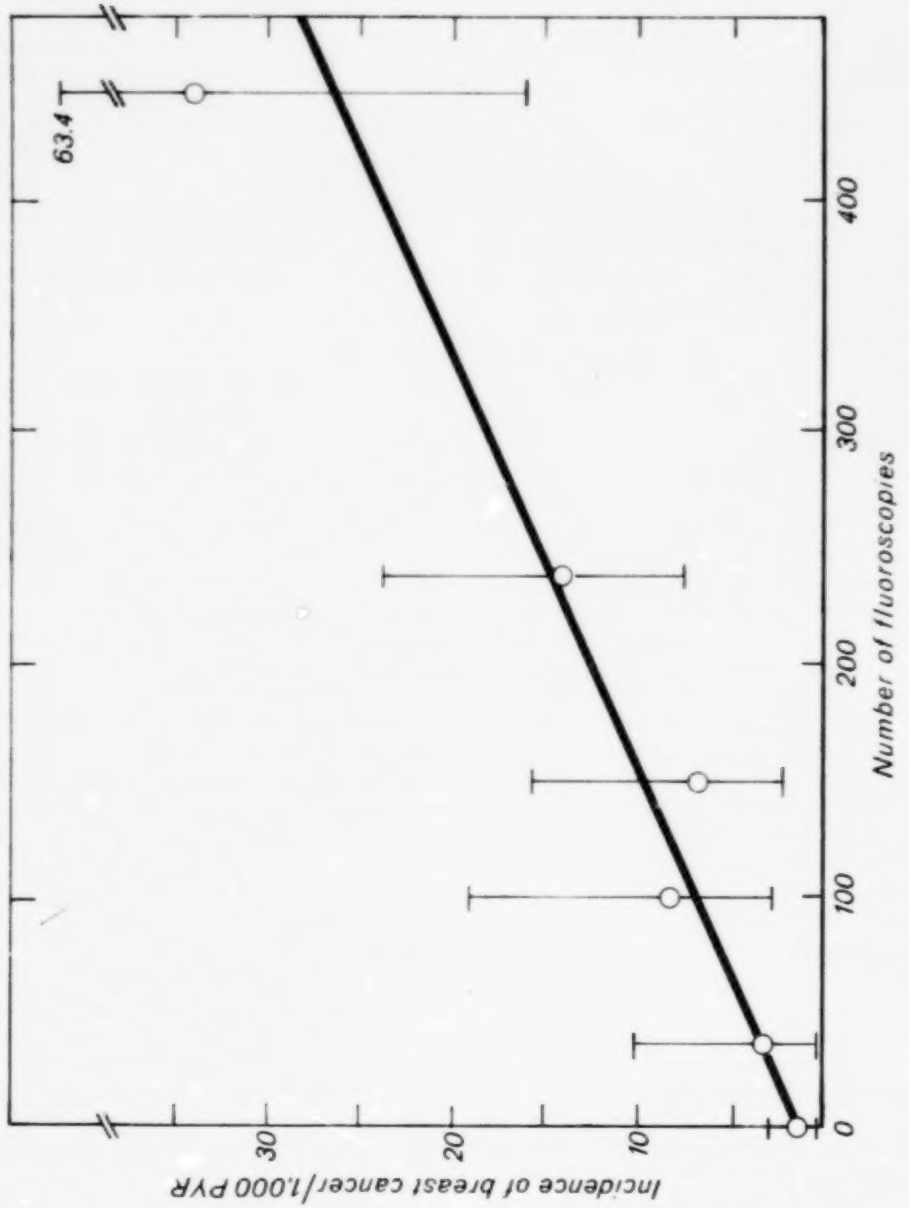

Figure e-1: Incidence of breast cancer per 10^3PYR (1966 data) against the number of fluoroscopies received. The error bars represent 90% confidence intervals, and the line is the best fitting weighted least squares regression line.

Table e-1 Basis of Risk Estimates for Breast Cancer

Study population	Reference	Type of radiation	Duration of radiation exposure	Duration of follow-up (years)		Period after irrad. on which risk estimates are based (years)	Number of subjects	Number of person-years	Dose (rads)		Age at irradiation (years)		Sex	Nature of control	Relative risk (O/E)	RBE	Percent increase in relative risk per rem	Absolute risk, deaths or cases/10^6/year/rem			Footnotes or other comments
				Range	Mean				Range, External	Mean, to tissue	Range	Mean						Best	Limits		
																			Lower 90%	Higher 90%	
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)	(13)	(14)	(15)	(16)	(17)	(18)	(19)	(20)		(21)
A-Bomb H + N 1945	18	γ + n	<10"	25	25	16-25	11,968	113,286	10-600	81	10 +	34	F	0-9 rads	$\frac{26}{12.9}$ = 2.0	1	1.2	1.4	.61	2.2	
																5	0.8	0.91	.39	1.4	RBE for n taken as 5, γ as 1.
A-Bomb H + N 1945	18	γ + n	<10"	25	25	20-25	11,968	59,787	10-600	81	10 +	34	F	0-9 rads	$\frac{19}{4.9}$ = 3.9	1	3.5	2.9	1.7	4.0	
																5	2.3	1.8	1.1	2.5	RBE for n taken as 5, γ as 1.
Fluoroscopy Series 1940-49	1,17	X	weeks to years	15-30	20	10-30	243	3,708	50-7000 R	121	0 to 560 + 76% 15-29	26	F	Patients not fluoroscoped	10.5	1	0.78	8.4	-	-	Confidence limits cannot be calculated, see text, p. 143-144
Mastitis Patients	3	X	min. to weeks	5-29	19	10-29	606	5,606	50-450 R	200	20-39	27	F	New York State	$\frac{11}{4.23}$ = 2.6	1	0.80	6.0	2.5	11.0	See text, p. 144

[a] This table does not provide a complete compendium of all studies; see text for selection. See Appendix VI for definitions of headings.

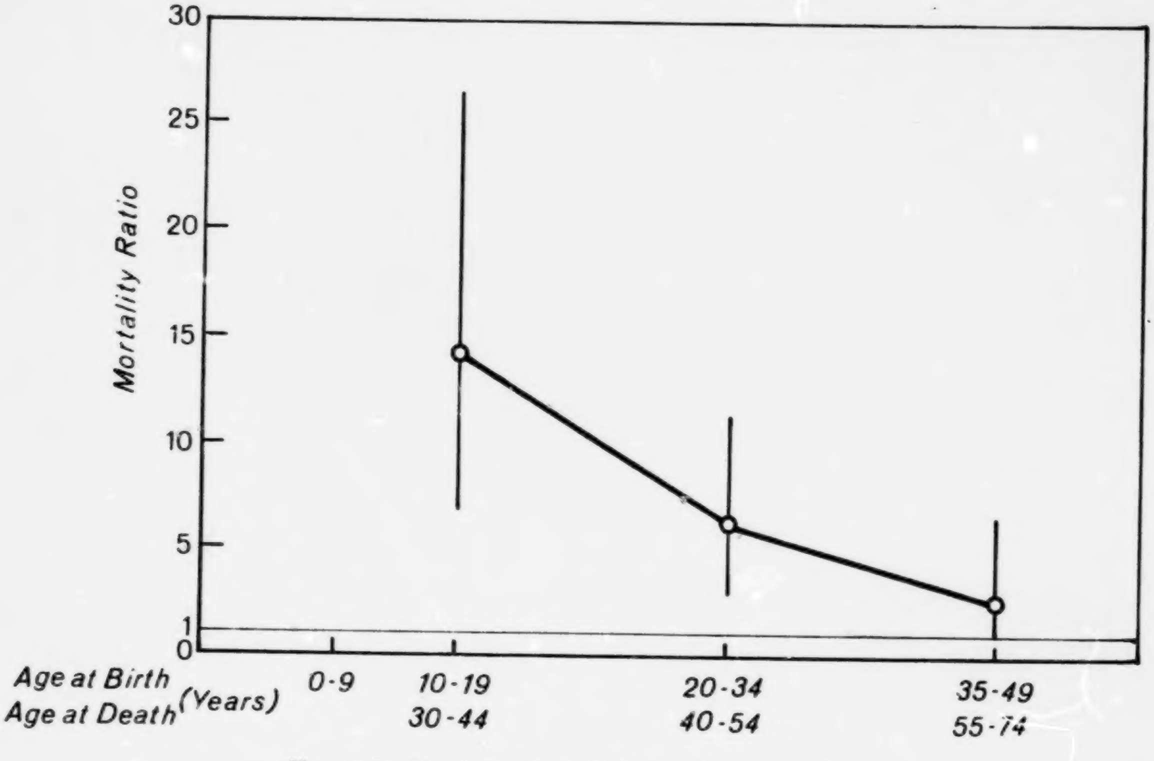

Figure e-2: Mortality ratios and 80% confidence intervals for deaths from breast cancer during 1965-70 in A-bomb survivors exposed to 50+ rads (from Ref. 13).

risk (since the spontaneous cancer incidence rises by a factor of approximately 4 in the United States from 30-44 to 55-74).

No data are available on the role of hormones in the pathogenesis of breast cancer in humans, aside from the marked sex differences, but it is probable that they are important in this regard, in view of their known role in the treatment of the disease and also since it has been shown that estrogen and mammotropic hormone are involved in the pathogenesis of radiation-induced breast cancer in irradiated rodents *(12)*.

Mechanisms

Although studies on human populations have been too limited thus far to contribute much to our understanding of the mechanism of radiation-induced mammary carcinogenesis, two tentative conclusions might be made. The first is that breast neoplasms, whether spontaneous or radiation-induced, appear to have a hormonal requirement. Thus, in the ABCC Life Span Study sample, no cases of breast cancer developed in the period 1965-70 in those aged 0-9 years ATB and exposed to 10+ rads, although 7 would have been expected had the absolute sensitivity been the same as in those 10-19 years ATB.

Second, the limited human data imply that the pathogenesis of radiation-induced breast cancer in women may resemble that in animals, in which the findings support the multistage theory of carcinogenesis *(15)*. It has been shown in rats, for example, that the mammary tissue itself must be irradiated for the primary, or initiating, step to occur *(14)*. The secondary step is promoted by proliferative stimulation of the damaged cells by one or more of the mammotropic hormones of the ovarian-anterior pituitary axis. The interaction between mammotropic hormone stimulation and x-irradiation has been shown to be synergistic in the induction of mammary neoplasms in the rat *(12)*. Experimental studies with rats have shown an RBE of approximately 2 for fast neutrons, for the induction of mammary gland tumors following exposure at relatively high doses. The RBE value for exposure at lower doses is higher, approximately 10 to 20 *(7)*.

Risk Estimates

The data in the risk estimate table (Table e-1) are drawn from the following sources:

A) *Breast Cancer in A-bomb Survivors:* Lines 1-2 of the table summarize the data obtained from death certificate analysis for the period 1960-70 *(13, 18)*. Since there was no excess of breast cancer deaths during 1960-64 in the irradiated (10+ rads) group, the data for 1965-70 have been analyzed separately (line 2). The best relative risk estimate from these data is a 3.5% increase in the cancer rate per rad and an absolute risk estimate of 2.9 deaths from breast cancer/10^6 women/year/rad if an RBE of 1 for neutrons is assumed. With an RBE for neutrons of 5, these estimates become 2.3% and 1.8/10^6/year/rad, respectively.

B) *Breast Cancer Following Multiple Fluoroscopies:* This was first reported by MacKenzie *(1)* and the study was later extended by Myrden and Hiltz *(16)*. It was found in both studies that women who were subjected to multiple fluoroscopies during artificial pneumothorax for pulmonary tuberculosis later developed breast cancer at a much higher rate than did similar women not subjected to the fluoroscopies. The Myrden and Hiltz study (*16*) has a total of 783 tuberculous women in their 15-25 year follow-up, of whom 22 out of 300 given pneumothorax treatment developed breast cancer compared with only 4 cases out of 483 with no pneumothorax treatment. More recent data (Myrden, personal communication) show the necessity of revising these figures to allow for many patients who died within 10 years of treatment and for extra cases of breast cancer which have developed subsequently. Table e-2 shows these data broken down by number of fluoroscopies received and the follow-up period. These data are also shown graphically in Figure e-1. The number of cancers in Table e-2 is correct up to September 1971, but the person years at risk are known at this point only to the time of the original study *(16)*. If it is assumed that all patients alive in 1965-66 were still alive in 1971, the number of persons years (PYR) in the non-fluoroscoped group increased from 3,250 to 4,665 and in the fluoroscoped group from 2607.5 to 3707.5. Undoubtedly, the 1971 figures are better for calculating the absolute

Table e-2. Follow-up details of the 306 non-fluoroscoped and the 243 fluoroscoped patients who survived at least 10 years.

			FOLLOW-UP PERIOD									TOTALS		Incidence[1] (Cancers per 10^3 PYR) with 90% C.I.
			10 - 14 yrs			15 - 19 yrs			20 - 25 yrs					
Number of Fluoros.	Mean # of Fluoros.	Number of Patients	Died	Surv.	With Ca	Died	Surv.	With Ca	Died	Surv.	With Ca	PYR[1]	Number of Cancers	
0	0	306	10	0	0	12	83	2	1	200	3	3,250	5	1.5 (0.6-3.2)
1-75	34.8	55	2	0	0	0	11	0	2	40	2	612.5	2	3.3 (0.6-10.3)
76-125	100.5	47	2	0	0	2	15	1	0	28	3	482.5	4	8.3 (2.8-19.0)
126-175	150.5	54	1	0	0	3	13	1	3	34	3	585	4	6.8 (2.3-15.6)
176-300	238	68	5	0	2	0	16	1	2	45	7	720	10	13.9 (7.5-23.6)
300+	453	19	1	0	0	1	3	2	1	13	5	207.5	7	33.7 (15.9-63.4)

[1] As discussed in the text the PYR are correct only to 1966 whereas the number of cancers is correct to 1971. This affects the incidence figures, which should be reduced by approximately 30% to compensate for this.

risk estimate and so have been used, even though they would tend to produce a slight underestimate of this risk. The relative risk of developing breast cancer in the fluoroscoped group compared with the controls is 6.73 or 6.79 depending on whether the 1966 or 1971 PYR are used. Since the majority of the patients had unilateral pneumothorax treatment, it follows that the breast on the treated side was exposed to more dose from the fluoroscopies than was the other. This means that the relative risk of developing breast cancer has to be adjusted to compensate for this inequality of dose. From the data published by Myrden and Hiltz *(16)*, it can be calculated that the relative risk should be increased by a factor of 1.55[1] bringing it to 10.5.

The main problem in developing a risk estimate from these (and MacKenzie's) data is the lack of a reliable radiation dose estimate. MacKenzie *(1)* tried to estimate the typical dose that might have been given and found that at the average setting of the x-ray equipment a dose rate of 22 to 55 R/min was delivered (depending on the presence or absence of a filter). Physicians were strongly advised never to exceed an exposure of 10 seconds, but longer exposures were apparently not uncommon. It is likely that the majority of patients were subjected to radiation during a fluoroscopy of from 10 to 30 seconds (Myrden, personal communication; Skavlem, personal communication). This range together with the range of 22 to 55 R/min leads to a mean dose per fluoroscopy of 10R with standard error limits of 5 to 20R. The mean number of fluoroscopies received by the women treated with pneumothorax and who survived for 10 or more years is 162, which gives an average dose estimate of 1,610 R. Since a few patients received more than 500 fluoroscopies (=5,000 R or 6,000 rads to the skin using a backscatter factor of 1.2), and three patients developed radiation dermatitis, this dose estimate seems reasonable. Owing to the soft nature of the x rays, it is probable that a further correction to the dose should be made to correct for the attenuation of the x rays through the tissues overlying the breast tissue. Assuming the breast tissue lies at a minimum of 1 cm below the skin surface, the maximum dose to breast tissue would be approximately 75% of the air dose. Hence, the average dose[2] estimate becomes 1,215 rads.

These calculations lead to a relative risk of a 0.78% increase in the spontaneous rate per rad and an absolute risk estimate of 8.4 cases/10^6/year/rad.

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[1] The correction factor has to take into account two phenomena:

(i) The unilaterally treated patients received some radiation to the breast on the non-treated side.

(ii) Some patients received bilateral treatment and, hence, had equal exposure to both breasts.

The factors for each of these phenomena can be calculated as follows:

(i) In the Myrden and Hiltz (16) study, 14 of the 17 patients who developed breast cancer following unilateral exposure, developed the tumor on the treated side. Assuming a linear dose effect curve and equal probability of developing cancer in either breast, it follows that this reflects the different doses to the two breasts. Hence, dose to "irradiated" breast/dose to "unirradiated" breast is 14/3 or 1/0.214. Since we need to calculate the probability of a woman developing cancer, the relative risk for the unilaterally treated patients must be increased by a factor of 2/1.214 or 1.65.

(ii) Of the 22 patients who developed cancer following pneumothorax treatment, 5 were bilaterally and 17 were unilaterally treated. Since the unilaterally treated patients would be expected to be underrepresented in the group of cancer patients since these women received less radiation from the fluoroscopy exposure, the true bilateral: unilateral treatment ratio should be 5: 17 x 1.65 or 5:28.

Assuming that the bilaterally treated patients have the correct relative risk, the final correction factor is:

$$\frac{5 \times 1 + 28 \times 1.65}{33} = 1.55$$

[2] It should be noted that although fluoroscopic procedures varied from place to place in Canada and the United States with respect to the patient either facing the x-ray tube or facing the physicians, in the Nova Scotia series the former position, i.e., the patient facing the x-ray tube, was adopted (1). This might well partially account for the fact that other centers have failed to report high incidences of mammary carcinomas subsequent to artificial pneumothorax treatment.

C) Breast Cancer Following Treatment for Postpartum Mastitis: Mettler et al. (*3*) described the 10 - 25 year follow-up of 606 women treated with x ray for acute postpartum mastitis. They found 13 cases of breast cancer against 5.86 expected. The majority of women (513/606) were aged 20 - 34 at the time of treatment and received an average air dose of 211 R to both breasts. Converting this dose to rads yields an average dose to both breasts of 200 rads, which gives rise to a relative risk estimate of a 0.61% increase per rad and an absolute risk of 3.1 cases/10^6/year/rad. However, these calculations ignore the fact that approximately half of the PYR occurred in the first 10 years of follow-up during which time only 2 cases of breast cancer developed (1.6 expected). Since a minimum latent period of 10 years is consistent not only with these data but also with the above studies, it is essential in calculating the risk estimates to derive new data excluding the first 10 years of follow-up both for the PYR and for the expected number of cases. This can be done from the age distribution of patients at first treatment, provided it is assumed that each age group has the same mean follow-up. Such a calculation gives a value of 5,606 for the PYR and an expected number of cases of breast cancer of 4.23 (from the age-specific cancer rates in upstate New York for 1958-60). These data lead to a relative risk estimate of a 0.80% increase in the cancer incidence per rad and an absolute risk estimate of 6.0 cases/10^6/year/rad.

A legitimate objection to the calculation of risk estimates from this study is the uncertainty as to whether the general population constitutes an adequate control; or in other words, does acute postpartum mastitis predispose to breast cancer? Although such acute infectious processes are not usually believed to be associated with subsequent development of cancer, women with so-called chronic cystic mastitis are more prone than the general population to have breast carcinomas. In this study, approximately half of the 38 women subjected to breast surgery for neoplasms were reported to have chronic cystic mastitis. What role this plays in the findings is not understood, but for lack of good evidence to the contrary, it has been supposed for purposes of risk estimation that the excess cases were radiation-induced and that the risk estimates are valid.

Summary

Despite the number of assumptions involved in calculating risk estimates and the paucity of cases in the above studies, the following tentative conclusions can be drawn:

(a) If an RBE of 1 for the neutron component at Hiroshima is assumed, the absolute risk estimates from the 4 studies are remarkably close. For example, if it is assumed that a factor of 2 can be applied to correct deaths from, to incidence of, breast cancer in Japanese women, then the estimated values of the absolute risk, in cases/10^6women/year/rad, are 6.0 for the Japanese study, and 8.4 for the two studies of Western populations. None of these is significantly different from any other. On the other hand, the relative risk estimates are significantly higher for the Japanese women, reflecting their much lower natural incidence of breast cancer, as compared with Western women.

(b) If an RBE of 5 for the neutron component in Hiroshima is assumed, then neither the absolute nor the relative risk estimates for the Japanese would appear to agree with those of the two Western studies.

(c) Since the two Western studies give close agreement, both in absolute and relative risk estimates, and since the major interest of this analysis is the development of risk estimates for the U.S., it seems appropriate to focus on these two series to obtain an overall best estimate of the risk. The high degree of uncertainty in the dose estimate for the fluoroscopy series makes this estimate less reliable than that from the post-partum mastitis patients, and so the value of 6 cases of breast cancer/10^6 women/rad (or rem) has been chosen as the best estimate of the absolute risk. Since the age-adjusted annual incidence of breast cancer in U.S. women is 72/10^5 (*17*), the above absolute risk corresponds to a doubling dose of 120 rads, or an 0.83% increase per rad in the spontaneous incidence. Reasonable high and low estimates might lie within a factor of 2 on either side of these values.

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f. Lung

Introduction

There has been a worldwide increase in the incidence of bronchial cancer within the last few decades, pointing to the sensitivity of the renewal cells of the respiratory epithelium to carinogenic influences in the environment (*1*). The increase in lung cancer is not uniform throughout the world, nor can it, in all instances, be directly correlated with cigarette smoking. Other factors such as air pollution evidently also play a role. These considerations are important because of the evidence that bronchial cancers associated with occupational irradiation may vary in frequency, depending on whether other environmental factors are also present. Radiation protection standards for the general public must allow for the possibility that a significant fraction of the human population will be exposed to cigarette smoke by direct inhalation, as well as to the other less well-defined environmental carcinogenic factors.

The principal series of radiation-induced lung cancers has been observed in underground miners exposed to radon decay products in the mine atmosphere. From the multiplicity of occupational exposure conditions that have been associated with an increased incidence of bronchial cancer, however, it is evident that many other types of carcinogens, besides radiation, can also induce bronchial cancer. Chemical agents included in this category are asbestos, chromium salts, mustard gas, hematite, nickel and arsenic compounds, and asphalt derivatives (*2-8*). Radon daughters and asbestos appear to be most strongly carcinogenic in association with cigarette smoking.

There has been considerable discussion of the comparability of the different types of tumors associated with environmental agents. The epidemiology and histologic types of these tumors have been reviewed by Berg *(9)* and Kreyberg *(10)*. The bronchial and parenchymal respiratory cancers in man are generally divided into two major classifications. The first group comprises adenocarcinomas of the bronchoalveolar type, as well as special types of tumors such as carcinoids. The second category includes epidermoid carcinomas and small- and large-cell anaplastic epithelial tumors of the proximal portion of the bronchial tree. The first group of tumors is the most common in nonsmokers, while the latter group of tumors are those particularly associated with cigarette smoking. The type associated with exposure to radiation, arsenic, nickel, chromium, hematite, mustard gas, and asbestos is similar to that associated with cigarette smoking *(4, 11)*, which is not astonishing inasmuch as cigarette smoking generally plays an important contributory role in their development. It should be emphasized, however, that there is considerable overlap in the distribution of the different types of lung cancers, regardless of the presence or absence of environmental factors.

A recent analysis by Saccomanno and colleagues *(12)* of 150 cases of lung cancer among uranium miners has shown that the predominant cancer types among individuals with the highest radon-daughter exposures are the small-cell and undifferentiated types, constituting about 75% of all lung cancers in the higher dose categories. The possibility exists that the cells of origin of the epidermoid cancers are different from those of the small-cell cancers *(13)*, but the existence of two such populations of origin in normal tissue remains to be established.

Because of the presence of a number of potential occupational carcinogens in the dust of underground mines, there has been some question as to whether radon and radon daughters constitute the principal cause of increased risk among these miners. Pertinent to this issue is the fact that underground mining *per se* does not necessarily lead to an increase of lung cancer risk, a fact that has been well documented for underground coal miners in the United Kingdom (*14*). A recent study has investigated 5,500 potash miners in New Mexico, working in mines not associated with elevated concentrations of radon-daughter products in the air, and has shown no increased risk in such below-ground miners as compared with above-ground workers (*15*); (in both groups excess cigarette smoking could account for the increased lung cancer compared to the general population). It is pertinent to point out that in those mining operations where a significant increase in respiratory cancer has been associated with inhalation of radon and its daugher products, the mineral constituents being mined were widely variable. Besides the uranium miners in Europe and the U.S.A. (*15, 16*), excess respiratory cancer risk has been found among underground metal miners (*17*), fluorspar miners (*18, 36*), and hematite miners (*5*). In each of these populations, there was occupational exposure to increased concentrations of radon which was also present in the mines. Thus, whether or not other agents such as arsenic, uranium, or fluoride may have been present in the air, the one constant relationship in these groups has been radon-daughter exposure and the incidence of lung cancer (*15*). In the early studies of the Bohemian pitchblende industry (*19*), some of the employees in milling operations developed lung cancer, as did miners, but their exposures to radon and radon daughters, while probably significant, are not known with accuracy. In the U.S., uranium mill workers have not experienced an increased risk of lung cancer (*15*), presumably because good ventilation minimizes their exposure to radon daughters.

Relationship of Cancer Rate to Radiation Exposure

In view of the importance of control of lung cancer among underground miners, especially in the uranium industry, vigorous efforts at establishing a dose-response relationship have been undertaken. In the U.S. a study of approximately 4,000 uranium miners has been carried out by the U.S. Public Health Service, particularly dated from 1957. A current report of this continuing study was submitted to an ad hoc subcommittee of the Advisory Committee to the Federal Radiation Council by Lundin, Wagoner and Archer *(20)*. In addition, a report to the Interagency Uranium Mining Review Group has recently been prepared *(15)*, with a summary of cases through September 1969. Finally, Dr. Archer has made available data on all cases of cancer in the uranium mining study group identified through March 1971.

Although most of the evidence relating radiation exposure to lung cancer in man pertains to internally deposited alpha-emitting radionuclides, such as radon daughters and thoron and its short-lived daughters, as summarized by Lundin and coworkers (*15*), there is some evidence of an excess lung cancer rate in individuals exposed to gamma and x radiation. Among the survivors of the atomic bombing in Hiroshima and Nagasaki, data are now available for the period up to 1970 *(21)*, which show the relative risk of cancer of the tracheobronchial tree for the period of 1955 to 1970 to be 1.4 times higher for doses of 10 rads or more than for lower doses. Difficulties exist in interpreting these data, however, one of which is the fact that in the control group (i.e., those farthest from ground zero) the observed cancer rate was about 50% higher than that expected for the Japanese at large. In addition, there is the question of neutron irradiation in the exposed individuals, which may have contributed significantly to the observed effects in view of the possibly high RBE of this component of the total dose.

An approximately two-fold increase in the relative risk of lung cancer was observed in the study by Court Brown and Doll *(22)* of patients with ankylosing spondylitis treated with x-ray therapy. In these cases large doses of x rays were delivered to the spine, and doses to the bronchial epithelium were estimated to average about 400 rads *(23)*.

In a study of patients with tuberculosis, whether active or inactive, an increase in lung cancer of from 5- to 10-fold was found in comparison to the incidence in the general population *(24)*. The possibility has been raised that the patients may have been exposed to fluoroscopy during treatment of the disease, and that this may account for their increased risk *(24)*. In the absence of specific exposure information, however, and in view of the fact that there could also be a relationship between tuberculosis itself and the likelihood of developing lung cancer (*25*), little emphasis can be given to this study at present.

The incidence of lung cancer in x-ray technicians has been compared with that in pharmacy and medical technicians in the U. S. military service during World War II (*26*). Out of approximately 13,000 individuals who were present in both groups, 17 deaths from respiratory cancer were observed among the x-ray technicians as compared with four among the other groups. This difference is highly significant, but when the groups were compared with appropriate U. S. mortality statistics, a total of 12.4 cancers was expected for the x-ray technicians, which was not significantly lower than the 17 cases observed. Thus the difference between groups may be due primarily to a decreased lung cancer incidence among the pharmacy and medical technicians, which is paradoxical and which complicates interpretation of the data.

The experience through 1967 for all of the various underground mining groups in which an increased risk of cancer has been found, has been summarized by Archer and Lundin *(27)*, and Archer has updated this summary to September 1969 in the report for the Interagency Uranium Mining Review Group *(15)*. Central to an interpretation of data from underground miners are a number of fundamental issues, which include the following: (a) What exposures to radon daughters have actually occurred? (b) What is the rad dose to the critical cells from radon daughters in the air? (c) Is an increased risk observed at a dose rate below that equivalent to continuous occupational exposure to one working level of radon and radon daughters? (d) Is the dose-response curve at low doses linear, is it concave downward (i.e., giving a higher risk per rad at lower cumulative doses than at higher cumulative doses) or does a true threshold for cancer production from a cumulative dose exist?

Considerable effort has been made to evaluate the radiation exposures of the various groups of miners in the Colorado Plateau area, with particular emphasis on previous underground mining experience not included in the category of uranium mining (a substantial number of the miners had such experience).

Absent or infrequent sampling of air of some of the mines, especially in the early exposure prior to 1950, makes estimates of cumulative dose only approximate at best, but it is unlikely that these estimates can greatly be improved at this time, and it is probable that in the aggregate the estimates of exposure are adequate to determine trends in the data. It should be emphasized that among these miners the dose rate was quite high in comparison to that in some of the other mining groups (about 10 Working Levels on the average, see below).

With regard to the relationship between the WLM and the rad dose to the basal cell layer of respiratory epithelium from inhalation of radon and radon daughters, the literature has been recently reviewed by Walsh *(28)* and by the Interagency Uranium Mining Review Group *(15)*, with essential agreement between both reviews. One "Working Level" (WL) in air is defined as any combination of short-lived radon daughters (through polonium-214, RaC′) leading to total emission of 1.3×10^5 Mev of alpha energy per liter, and the cumulative measurement of Working Level Month (WLM) is defined as exposure at the rate of 1 WL for 170 hours. There has been criticism of the WL as an exposure index, because the state of equilibrium of the various nuclides in the chain is critical, especially with regard to the fraction present as free ions. This latter criticism remains valid, but it is fair to say that samples of mine air usually show relatively little contribution of unbound radon daughters.

Estimates of the rad dose/WLM for basal cell layers of different segments of the bronchial epithelium have varied widely, from less than 0.1 rad/WLM to as much as 20 rad/WLM *(37)*. A critical factor in these estimates is the thickness of the epithelial and mucous layers, an uncertain quantity in smokers with some degree of chronic bronchitis. The unpublished studies of Gastineau *(20)* indicate that the normal epithelium of segmental and more proximal bronchi, where most radiogenic cancers have arisen, is thicker than had previously been assumed.

On the basis of the present evidence, 1 rad/WLM is probably close to the upper limit for a reasonably uniform dose to the basal cell layer of the epithelium of the larger bronchi on a probabilistic basis. In the presence of existing chronic bronchitis, the dose factor may well be substantially lower, owing to increased thickness of the mucous layer as well as of the epithelium, and thus a figure of 0.5 rad/WLM has been adopted for this report. It should be emphasized that uncertainties in this value are probably greater than for the working level measurements themselves in determining risks per rad for the mining populations.

So far as a limiting dose rate is concerned, the question is whether continuous exposure to less than 1 WL has been found in miners to be associated with increase in lung cancer risk. The problem is related to the possible influence of dose rate on latent period, and if latent periods of 20 to 30 years are found at the lowest exposures, no mining group has been under observation with *known* exposures at these levels for a long enough time to provide a definitive answer. The metal miners studied by Wagoner *et al.* *(17)* showed a cancer rate about three times that expected, with exposures at the time of the study well below a concentration of 1 WL, but these authors indicate that earlier exposures before the mines were ventilated may well have been higher. The hematite miners studied by Boyd *et al.* *(5)*, who have shown a risk of about 1.7 compared with controls, worked in mines where the radon concentrations are equivalent to WL concentrations of 1 WL or less, but until measurements of actual radon daughter exposures and the influence of the hematite itself are determined, no final conclusion is possible. For the Colorado Plateau uranium miners in the lowest cumulative WLM exposure category whose dosage was usually received from several short periods of high working level exposures, no significant excess of cancer has appeared as yet (see below).

The question of the linearity of the dose-response relationship and whether a true threshold is present has been discussed thoroughly by the *ad hoc* Committee report *(20)* and the Interagency Uranium Mining Review Group report *(15)*. At present, the fact that the lowest exposure group shows only a slight increase in cancer rate above that expected makes the Colorado Plateau group inadequate to resolve this issue. Inspection of the composition of the study population indicates that the population at risk in this dose range (120 WLM) is now so small as to make it unlikely that even future follow-up will settle the matter.

There has been observed in the U.S. Colorado Plateau workers an inverse relationship between cumulative radiation dose and the latent period for cancer after initial exposure in the mines, but this effect is not very striking at the present time. The relationship of cigarette smoking to the latency period for lung cancer among uranium miners is not known.

Experimental Bronchial Cancer in Animals

A large body of experimental work has now been assembled relating the occurrence of lung cancer to ionizing radiation in animals, and has been summarized by Sanders, *et al. (29)* and by the Interagency Uranium Mining Review Group (*15*). Although lung tumors are readily induced in animals by radiation exposure, not all of these may be relevant to the human disease, since peripheral adenocarcinomas are much more likely to occur in animals from whatever inciting stimulus is applied than are tumors comparable to squamous cell tumors in man.

For alpha-emitters the lowest cumulative dose at which a rise in lung cancer has been observed experimentally was in rats given polonium-210 with a sodium chloride aerosol by inhalation *(30)*. In this experiment one squamous cell cancer occurred after 70 rads cumulative mean lung dose, and the dose-incidence relation was approximately linear at higher doses. For beta-emitters the lowest dose associated with cancer induction was approximately 600 rads, in rats given cesium-144 salts by intratracheal instillation *(31)*. In these experiments the dose-response curve appeared to be curvilinear (concave upward). An inherent difficulty in animal experiments, of course, is the short life span of the small rodents usually used and thus the fact that only the cancers with short latent periods may be detected by this approach, a limitation which might be expected to produce a curvilinear dose-response curve of the kind observed.

An important issue is whether local, or "hot spot", doses are more effective in producing cancer in the respiratory tract than is uniform radiation exposure to the entire epithelium. Experiments of Grossman and Little (*32*), in which polonium-210 chloride was given intratracheally, with and without hematite particles, are pertinent to this issue. Previous experiments have shown that when polonium-210 was given simultaneously with hematite, the incidence of tumors was related to the polonium concentration, with a latent period as short as 15 weeks, depending on the total cumulative alpha radiation dose (*33*). In the more recent study, polonium and hematite were given either on alternate days or no hematite was given at all. Since polonium solution alone was as effective as polonium given with hematite, it may be inferred that a higher localized dose from alpha particles was not more cancerogenic than the same mean tissue dose delivered more uniformly to critical cells.

Host Factors and Mechanism of Action of Radiogenic Lung Cancer

It has been pointed out above that a number of environmental factors may influence the development of bronchial cancer in individuals exposed to radiation. The lower incidence of lung cancer in females than in males may presumably be due in part to differences in exposure to these factors, the most obvious of which is cigarette smoking. In addition, however, the contribution of other environmental factors, such as carcinogens in air pollution, occupational inhalation of asbestos fibers, or systemic carcinogenic factors such as nitrosamines must be considered (*34*). Other host factors, such as may influence susceptibility to chronic lung disease, for example, α_1-antitrypsin deficiency, may be mentioned but are not yet adequately evaluated in relation to cancer.

It has been postulated that cancer production in the bronchial epithelium involves metaplastic changes in the tissue induced by nonspecific irritants, such as phenols or sulfur dioxide exposure. That is, a chronic inflammation is established in which the carcinogenic potential of inhaled carcinogens is subsequently brought out. In this case the transformation by initiators, such as ionizing radiation, becomes manifest in an overt cancer, possibly arising at several points in the lungs simultaneously. An important unresolved issue is the question of whether the radiation exposure to local areas is the critical datum or whether an effect extending over the entire respiratory epithelium is more likely to lead to cancer. This is important because lung cancers usually arise at bifurcations of the bronchial tree. Most analyses have concluded that the issue is basically a probabilistic one, in that a more widespread exposure is likely to subject more cells to the carcinomatous transformation. Also at issue is the critical number of cells which must be affected within a single region, and various theoretical models have been applied to this, such as that of Bevan and Haque (35), whose speculative analysis concludes that somewhere between 15 and 20 cells in a particular region must be traversed by alpha radiation in order to produce the cancer transformation.

Summary of Human Data and Estimates of Risks of Bronchial Cancer From Radiation

Tables f-1 and f-2 summarize data obtained in six human populations in which it is possible to estimate the risk of lung cancer from radiation exposure. The data for the U.S. uranium miners, Newfoundland fluorspar miners, and the Hiroshima and Nagasaki survivors have been analyzed in terms of dose-response relationships, since it has been possible to subdivide these groups by dose categories. The dose response data are given in Figs. f-1, f-2, and f-3. In calculating the slope of the curve on each figure, the data points are weighted for the number of person-years at each point. For the first two mining groups, a straight line through the origin provides the best fit of the data, as might be expected for alpha-radiation exposure. In the case of the Japanese survivors, the four dose levels give somewhat erratic results, but the lowest dose range (10-49 rads) gives a higher risk than would be predicted for a linear fit to all the points, and thus there is no evidence of a "threshold" for this group.

The underground metal miners and the thorotrast patients are not considered to be as reliable for risk estimates as the other groups, because the dose estimates to the bronchial epithelium are even more uncertain than in the other study groups. For this reason they have been excluded from the following summary (although their inclusion would not greatly alter the results).

SUMMARY OF RISK ESTIMATES FOR BRONCHIAL CANCER

Adults only, and with cigarette smoking assumed to be characteristic of these populations.

	Absolute Risk Cases/10^6/years **per rem*** **Mean Bronchial Dose**	**Relative Risk** % Increase in Rate/Yr. **per rem*** **Mean Bronchial Dose**
Uranium Miners (white only)	0.63	0.18
Fluorspar Miners	1.61	0.61
Spondylitis Patients	1.2	0.19
Hiroshima & Nagasaki Survivors	0.60	0.19
Average	1.0	0.29

*Conversion to rem based on an RBE of 10 alpha particles (miners) and 5 for neutrons (Hiroshima and Nagasaki survivors), with the fraction of the rad dose assigned to neutrons taken from the T65 calculations.

Table f-1

Basis of Risk Estimates for Lung Cancer*

Study population	Reference	Type of radiation	Duration of radiation exposure	Duration of follow-up (years)		Period after irrad. on which risk estimates are based (years)	Number of subjects	Number of person-years	Dose (rads)		Age at irradiation (years)		Sex	Nature of control	Relative risk (O/E)	RBE	Percent increase in relative risk per rem	Absolute risk, deaths or cases/ 10^6/year/rem			Footnotes or other comments
				Range	Mean				Range, External	Mean, to tissue	Range	Mean						Best	Limits		
																			Lower 90%	Higher 90%	
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)	(13)	(14)	(15)	(16)	(17)	(18)	(19)	(20)		(21)
Uranium miners 1920-68	15	α	years	7-50	17	6th - 50th	4,146	47,990	< 60- 4,000	468	20- 60+	C 45	M	Arizona, Colorado, N. Mexico, Utah	$\frac{135}{16.0}$ = 8.4	10	.16	.53	.46	.60	See footnote (b)
Uranium miners white 1920-68	15	α	years	7-50	17	6th - 50th	3,366	38,622	< 60 - 4,000	475	20 - 60+	C 45	M	Arizona, Colorado, N. Mexico Utah	$\frac{130}{13.9}$ = 9.4	10	.18	.63	.55	.72	See footnote (b)
Uranium miners non-white 1920-68	15	α	years	7-50	17	6th - 50th	780	9,368	< 60 - 4,000	441	20 - 60+	C 45	M	Arizona, Colorado, N. Mexico Utah	$\frac{5}{2.1}$ = 2.4	10	.03	.07	.01	.17	See footnote (b)
Fluorspar miners 1935-63	36	α	years	5-33	26	11th - 33rd	C 800	10,890	15 - 1,000	277	17 - 60+	C 45	M	New Found- land	$\frac{51}{2.83}$ = 18.0	10	.61	1.6	1.3	1.9	
Metal miners	17	α	years	26-37	C 30	16th - 37th+	1,759	25,033	> 50 - 500	172	17 - 60	C 40	M	State Vital Statistics	$\frac{45}{16.1}$ = 2.8	10	0.10	.67	.48	.90	

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[a] This table does not provide a complete compendium of all studies; see text for selection. See Appendix VI for definitions of headings.

[b] Data have been updated to 1971 by adding cases provided through the courtesy of Dr. Victor Archer. Five cases in the series have been deleted, one (case 55) because his cancer appeared before five years after beginning underground mining, and four (cases 95, 121, 122, and 148) because the diagnosis of lung cancer did not have adequate confirmation. All other cases, including those still living, have been included. The number of person-years has been increased to include the period to September 1971 by the assumptions that all miners remain in the dose category at exit in 1968, and no change in the cumulative dose category occurred from 1968 to 1971, since few men are still mining. Mean doses are calculated from the six dose levles, weighted for person-years in that dose-range, and on the assumption that 1 WLM = 0.5 rad to the bronchial stem cell layer. The expected rates are uncorrected for differences between the miners and the general population with respect to cigarette smoking or urban residence, two corrections which are opposite in direction. The expected rates have beer calculated to include the 1968 to 1971 period.

Table I-2

Basis of Risk Estimates for Lung Cancer

Study population	Reference	Type of radiation	Duration of radiation exposure	Duration of follow-up (years)		Period after irrad. on which risk estimates are based (years)	Number of subjects	Number of person-years	Dose (rads)		Age at irradiation (years)		Sex	Nature of control	Relative risk (O/E)	RBE	Percent increase in relative risk per rem	Absolute risk, deaths or cases/ 10^6/year/rem			Footnotes or other comments
				Range	Mean				Range, External	Mean, to tissue	Range	Mean						Best	Limits		
																			Lower 90%	Higher 90%	
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)	(13)	(14)	(15)	(16)	(17)	(18)	(19)	(20)		(21)
Thorotrast systemic injection 1935-56	36	α	years	11-35	20	0 - 35th	921	14,700	?	C 50	< 4 - 65+	C 35	M & F	Portugal	$\frac{5}{1.12}$ = 4.5	10	0.69	.53	.18	1.1	See footnote (b)
Spondylitis Patients 1935-54	4,5	X	days to years	5-27	11	6th - 27th	14,554	89,432	250-2,750	400	15 - 55+	?	M & F	England & Wales	$\frac{96}{54.2}$ = 1.8	1	0.19	1.2	0.82	1.6	84% male
A-bomb H + N 1945	21	γ + n	< 10"	25	25	16th-25th	19,472	177,055	10 - 600	86	10+	35	M & F	0-9 rads	$\frac{71}{56.8}$ =	1	.29	.93	.08	1.8	
															1.2	5	.19	.60	.05	1.2	RBE for n taken as 5, γ as 1.

[a] This table does not provide a complete compendium of all studies; see text for selection. See Appendix VI for definitions of headings.

[b] Person-years have been corrected for a five-year latent period and to take account of the high mortality rate in this group of patients. The dose estimates are from Grillmeyer and Muth, Health Physics 20:409, 1971, particularly Figure 8 with corrections for the mean volume of thorotrast given (30 ml) and attenuation of the dose to the basal layer of the lobar bronchi. The expected number of cases has been taken from the original publication; it is not clear whether correction for a latent period was applied. If not, the risk estimates are too low.

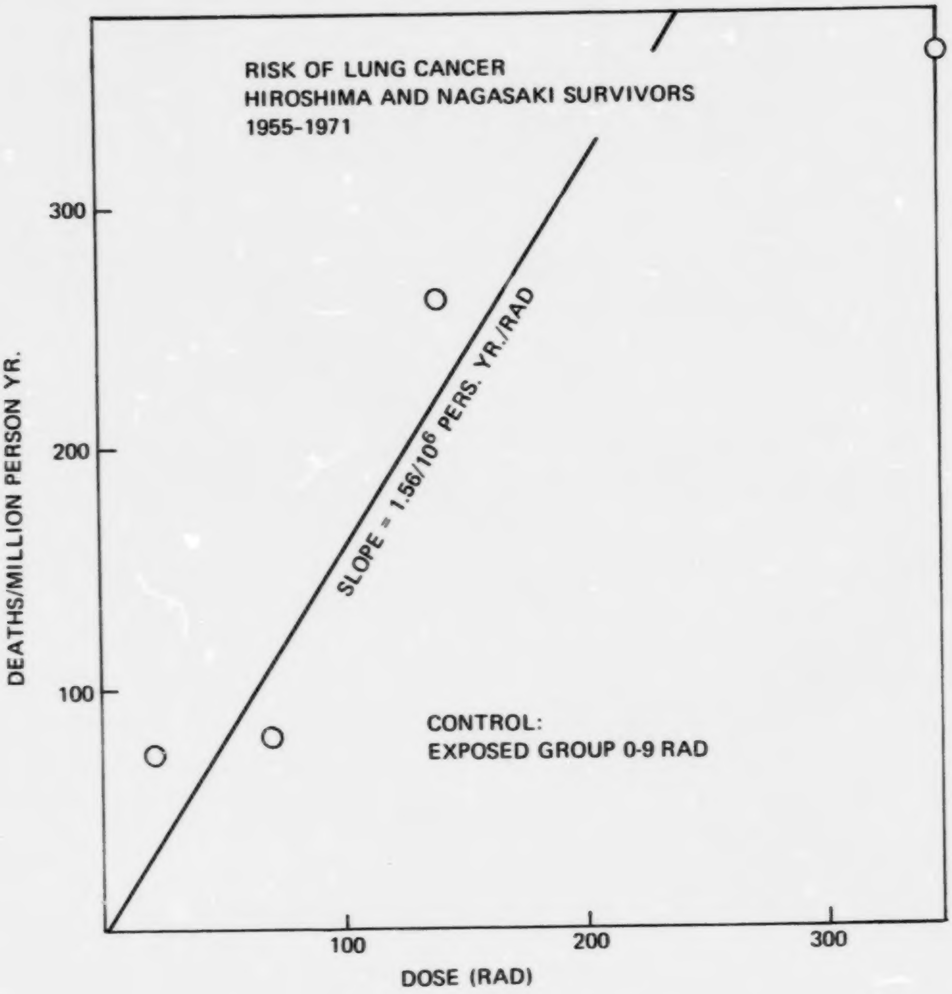

Fig. f-1: Dose-response data for lung cancer in Hiroshima-Nagasaki survivors (*21*).
Ordinate: Excess deaths per million person years.
Abscissa: T65 mean skin dose in rad. Correction of the dose for attenuation and for a neutron RBE of 5 gives rem values close to the doses shown. These data differ from those given in Table f-1 because they cover a different time period, and are given only as an approximate indication of the dose-response experience up to the present time.

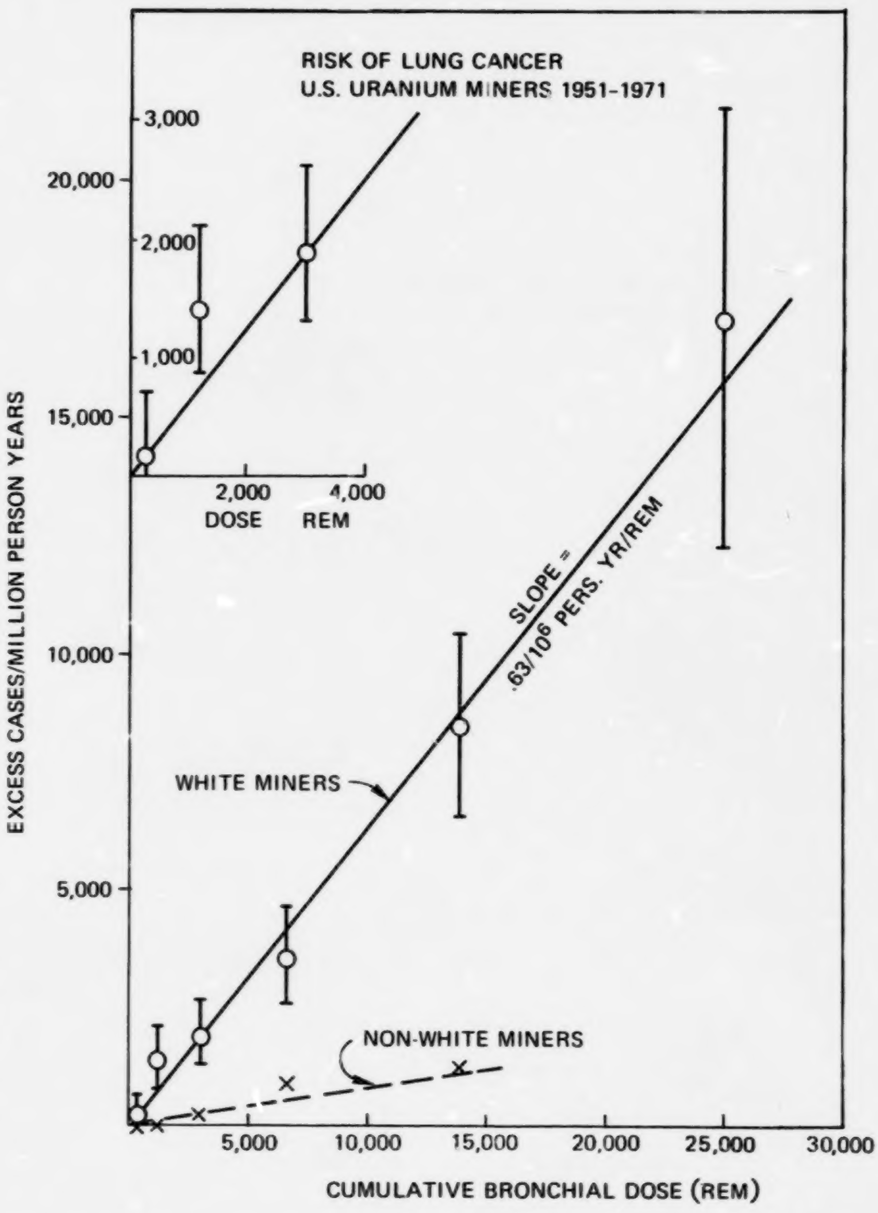

Fig. f-2: Dose-response data for lung cancer in U. S. uranium miners (Ref. 15, with added cases from Dr. Victor Archer).
Ordinate: Excess cases per million person years.
Abscissa: Rem dose to bronchial epithelium, calculated on basis that 1 WLM=5 rem.
Insert: Lowest dose range for white miners.
Error bars for white miners include 90% range for Poisson statistics (Appendix IV).

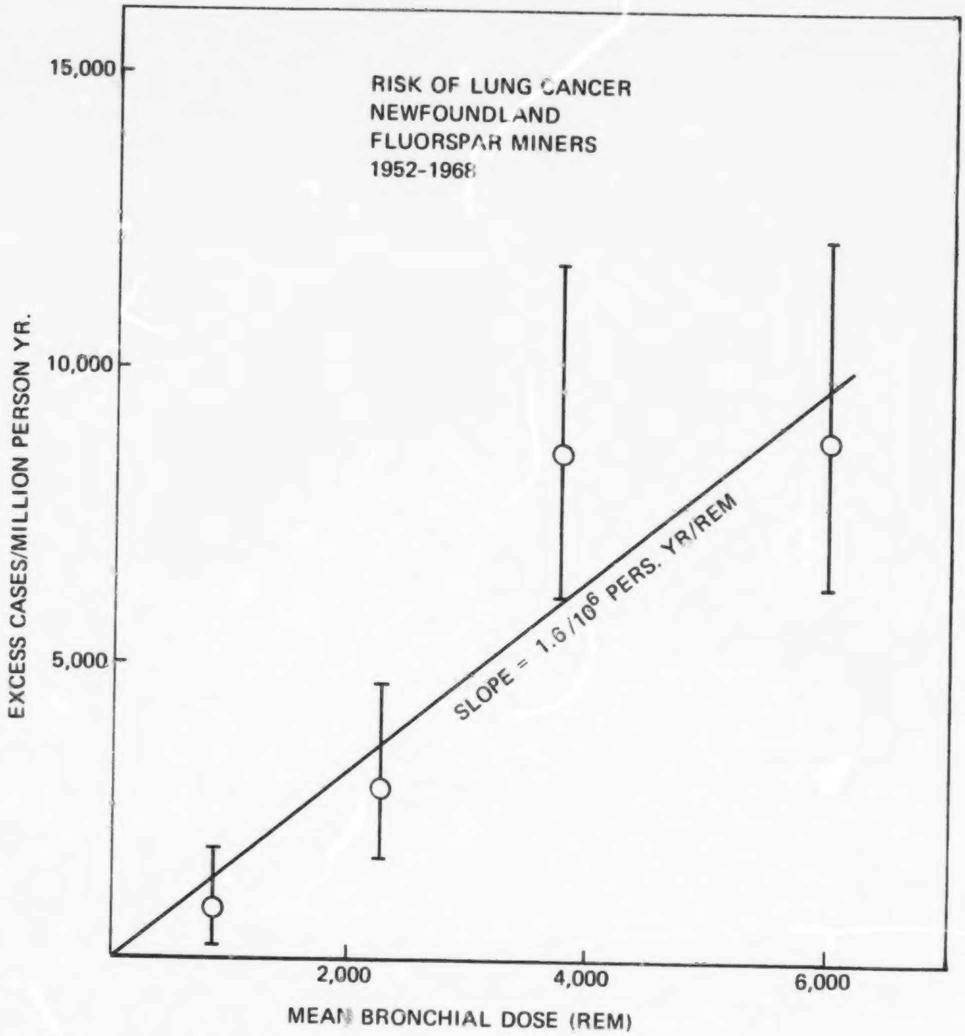

Fig. f-3: Dose-response data for lung cancer in Newfoundland fluorspar miners (36, Fig. 2).
Ordinate: Excess cases per million person years.
Abscissa: Mean bronchial dose, calculated on basis that miners were exposed at 5 WL, and 1 WLM = 5 rem.
Error bars include 90% range based on Poisson statistics (Appendix IV).

There is fairly good agreement among these four studies in the absolute risk calculated, when the RBE corrections are applied. On the other hand, the relative risk estimates for the fluorspar miners are somewhat divergent. The fluorspar miners give higher risk values than the U.S. uranium miners but a number of factors may account for this difference. These include: a) the fluorspar miners have been followed for a longer period, b) they are probably heavier smokers than the U.S. miners, and c) the U.S. data includes the period 5-10 years after beginning uranium mining, at a time when the risk is lower, while the risk estimates for the fluorspar miners are obtained over a period beginning, on the average, ten years after beginning underground mining. The possibility also exists that fluorspar acts as a cocarcinogen to increase the apparent risk in the fluorspar miners.

All four of these groups are still under investigation, and it is probable that because of the relatively long latent period for lung cancer, the rates calculated will rise as further cases develop. This is particularly true for the spondylitis patients. It is possible, therefore, that in the final analysis the absolute risk in these groups will approach $2/10^6$/year/rem and the relative risk reach 0.5% or higher. For the three groups (miners and Japanese survivors) in which up-to-date information is available, it is significant that many new cases have been added during the past few years.

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g. Other Neoplasms of Specific Types

A variety of neoplasms other than those mentioned above have been reported to occur in excess following irradiation. The neoplasms include lymphomas, carcinomas of the pharynx, carcinomas of the stomach, carcinomas of the pancreas, carcinomas of the paranasal and mastoid sinuses, cholangiomas and hemangioendotheliomas of the liver, tumors of salivary glands, and miscellaneous neoplasms of other types and sites (1, 2).

Data on stomach cancer (Table g-1) may be drawn from atomic bomb survivors and patients treated with x rays for ankylosing spondylitis. Analysis of the A-bomb data shows that there was no evidence of any radiation induced cases of stomach cancer in those survivors exposed to 10 or more rads in the period from the 16th to the 25th year after irradiation. Restriction of the analysis to the latter half of this period (i.e., 20-25 years after the bomb) still fails to indicate any excess cases (the relative risk for the 10+ rad group being 0.98). Analysis of the data from patients treated with x rays for ankylosing spondylitis shows a significant excess of stomach cancers occurring 6-27 years after irradiation. The best estimate of the absolute risk from these data is 0.32 to 0.64 deaths/10^6/year/rem depending on whether a value of 500 rads or 250 rads is used for the mean dose to the stomach. However, the possibility remains that the excess number of cases was not due to radiation but arose from selective factors associated with the disease process or its treatment.

An analysis of all G.I. cancers excluding those of the stomach is shown in Table g-2. The data again are taken from the atomic bomb survivors and the patients treated for ankylosing spondylitis. The mean dose to the relevant organs in the spondylitics patients is assumed to be the same as that for the stomach, i.e., lying between 250 and 500 rads. This dose range gives rise to a best estimate of the absolute risk varying from 0.22 to 0.44 deaths/10^6/year/rem. Again, the same limitation as discussed above applies to the data from the spondylitics patients.

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Table g-1

Basis of Risk Estimates for Stomach Cancer

Study population	Reference	Type of radiation	Duration of radiation exposure	Duration of follow-up (years)		Period after irrad. on which risk estimates are based (years)	Number of subjects	Number of person-years	Dose (rads)		Age at irradiation (years)		Sex	Nature of control	Relative risk (O/E)	RBE	Percent increase in relative risk per rem	Absolute risk, deaths or cases/ 10^6/year/rem			Footnotes or other comments
				Range	Mean				Range, External	Mean, to Tissue	Range	Mean						Best	Limits		
																			Low 90%	High 90%	
A-bomb H + N 1945	3	γ + n	<10"	25	25	16th-25th	23,979	225,675	10-600	82	0-80+	29	M & F	0 - 9 rads	$\frac{222}{221.0}$ = 1.00	1	0.0	0.06	0.0	1.4	
																5	0.0	0.04	0.0	0.86	RBE for n taken as 5, γ as 1.
Spondylitis Patients 1935-54	4	X	days to years	5 - 27	11	6th-27th	14,554	89,432	250 - 2750	250	15 - 55 +	36	M & F	England and Wales	$\frac{38}{23.6}$ = 1.61	1	0.24	0.64	.30	1.1	84 % male See footnote (b)
										500							0.12	0.32	.15	.53	

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[a] This table does not provide a complete compendium of all studies; see text for selection. See Appendix VI for definitions of headings.

[b] The value of 250 to 500 rads for the estimate of the mean dose to the stomach was derived by the Committee. A full description of this derivation is given in Appendix V. The upper and lower halves of the split line show the risk estimates using a mean dose estimate of 250 and 500 rads respectively.

Table g-2

Basis of Risk Estimates for all G. I. Cancer Except Stomach

Study population	Reference	Type of radiation	Duration of radiation exposure	Duration of follow-up (years)		Period after irrad. on which risk estimates are based (years)	Number of subjects	Number of person-years	Dose (rads)		Age at irradiation (years)		Sex	Nature of co.trol	Relative risk (O/E)	RBE	Percent increase in relative risk per rem	Absolute risk, deaths or cases/ 10^6/year/rem			Footnotes or other comments
				Range	Mean				Range, External	Mean, to tissue	Range	Mean						Best	Limits Lower 90%	Limits Higher 90%	
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)	(13)	(14)	(15)	(16)	(17)	(18)	(19)	(20)	(20)	(21)
A-bomb H + N 1945	3	γ + n	10"	25	25	16th-25th	23,979	225,675	10-600	82	0-80+	29	M & F	0-9 rads	$\frac{156}{142}$ = 1.10	1	0.12	0.76	0.0	1.8	RBE for n taken as 5, γ as 1.
																5	0.08	0.48	0.0	1.2	
Spondylitis Patients 1935-54	4	X	days to years	5-27	11	6th-27th	14,554	89,432	250-2,750	250	15-55+	36	M & F	England and Wales	$\frac{20}{10.1}$ = 2.0	1	0.40	0.44	0.20	0.76	84% male
										500							0.20	0.22	0.10	0.38	See footnotes (b) and (c)

[a] This table does not provide a complete compendium of all studies; see text for selection. See Appendix VI for definitions of headings.

[b] The 20 observed deaths in this category comprise 5 cancers of the pharynx, 3 of the esophagus, and 12 of the pancreas.

[c] The same dose estimate as that derived for the stomach (Appendix V) has been used in this case. The split line in the risk estimate column shows the estimate using the two extreme values of the mean dose; 250 rads and 500 rads for the upper and lower halves of the line respectively.

h. All Cancers Other Than Leukemia

Tables h-1 and h-2 show the data for all cancer excluding leukemia, the sources again being the A-bomb survivors and the patients treated with x rays for ankylosing spondylitis. The data from the A-bomb survivors are derived from deaths occurring from 1960 through 1970 and are grouped by age at the time of the bomb (ATB). These data are also shown in graphical form in Figures III-1 and III-2, and demonstrate the apparent higher relative sensitivity to cancer induction of persons irradiated when very young (0-9 year old). The risk estimates obtained from the patients treated for ankylosing spondylitis can be seen to be compatible with the pooled data from all survivors who were aged 10 or more ATB. These observations indicate that the eventual total number of deaths from solid tumors induced by a given dose may well exceed those from leukemia by a factor of 5 or more.

2. Cancer Following Irradiation Before Conception or During Intrauterine Life

First Reports

In 1956 Stewart and her associates (1) published a preliminary report describing a two-fold excess of leukemia and other cancer among children whose mothers received diagnostic x radiation during the relevant pregnancy. Two years later a definitive report was published *(2)*. It showed that the risk of cancer among the irradiated group was about doubled for six of eight categories of childhood neoplasia, the exceptions being myeloblastic leukemia and lymphoma.

The history of irradiation was obtained by interview from mothers of a) 619 children who died of leukemia, b) 680 who died of other cancer, and c) an equal number of controls (children without cancer) matched by age, sex, and locality. All deaths in the case-group occurred before 10 years of age, 1953-1955.

Confirmation

In 1962 MacMahon *(3)* reported similar results from a study with objective evidence of maternal radiation exposure rather than reliance on perhaps unavoidably biased interviews. Through the use of obstetric records in 37 large maternity hospitals in New England, for the period 1947-54, he determined the frequency of diagnostic x-ray study of the mother's abdomen during pregnancy for 569 children who subsequently died of cancer, as compared with a 1% systematic sample of all other births in the same hospitals. (Table 2-1). The results indicated that following such exposure the relative risk of childhood leukemia was increased by 40%, cancer of the central nervous system by 60% and all other cancer by 50%. No relation was found between neoplasia and recorded complications of pregnancy. The oncogenic effect of x ray seemed to be exhausted by eight years of age in contrast to its persistence through the entire span (up to 10 years of age) in the study of Stewart et al. MacMahon and Hutchison *(4)* later noted, in comparison these results with all others available to that date, that those showing no relation to x-ray exposure, including a prospective study by Court-Brown, Doll, and Hill *(5)*, lacked power to reveal an increase in relative risk of only 40-60% because of their relatively small sample sizes. Subsequently, a prospective pilot study by Diamond and Lilienfeld *(6)*, involving follow-up of about 20,000 children exposed to diagnostic radiation *in utero* and 40,000 controls, revealed among whites "a nearly two-fold increased risk of dying (from all causes) during their first 10 years of life." No excess occurred among the black children, who comprised about half the sample studied. Leukemia caused the deaths of six white children as compared with two expected; no such deaths occurred among *in utero* exposed black children. Neither ethnic group experienced an excess of other cancers.

Both Stewart and MacMahon showed that the relative risk of developing cancer following fetal diagnostic irradiation is elevated even in the first two years of life. The relative risk in both studies rises after this time, to reach a maximum for children dying at ages 6-7. In the MacMahon study *(3)*, the oncogenic effect of x rays seemed to be exhausted by 8 years of age (analysis of the data indicates that one can state with 95% confidence that the relative risk for those dying at 8 years old or later does not exceed 1.05), in contrast to its persistence through the entire span (up

Table h-1

Basis of Risk Estimates for all Cancer Except Leukemia

Study population	Reference	Type of radiation	Duration of radiation exposure	Duration of follow-up (years)		Period after irrad. on which risk estimates are based (years)	Number of subjects	Number of person-years	Dose (rads)		Age at irradiation (years)		Sex	Nature of control	Relative risk (O/E)	RBE	Percent increase in relative risk per rem	Absolute risk, deaths or cases/10^6/year/rem			Footnotes or other comments
				Range	Mean				Range, External	Mean, to tissue	Range	Mean						Best	Limits		
																			Low 90%	High 90%	
A-bomb H + N 1945	2	γ + n	<10"	25	25	15 - 25		48,620	10 - 600	69	0 - 9	5	M & F	0 - 9 rads	6/2.1 =	1	2.7	1.2	0.11	2.2	
															2.9	5	1.7	0.75	0.07	1.4	RBE for n taken as 5, γ as 1.
A-bomb H + N 1945	2	γ + n	<10"	25	25	15 - 25		53,385	10 - 600	102	10-19	15	M & F	0 - 9 rads	23/16.9 = 1.4	1	0.36	1.1	0.0	2.6	
																5	0.23	0.72	0.0	1.7	RBE for n taken as 5, γ as 1.
A-bomb H + N 1945	2	γ + n	<10"	25	25	15 - 25		50,120	10 - 600	87	20-34	28	M & F	0 - 9 rads	85/63.9=	1	0.38	4.8	1.6	8.2	
															1.3	5	0.24	3.1	1.0	5.2	RBE for n taken as 5, γ as 1.
A-bomb H + N 1945	2	γ + n	<10"	25	25	15 - 25		53,851	10 - 600	78	35-49	42	M & F	0 - 9 rads	286/251=	1	0.18	8.4	2.2	14.7	
															1.1	5	0.12	5.4	1.4	9.4	RBE for n taken as 5, γ as 1.
A-bomb H + N 1945	2	γ + n	<10"	25	25	15 - 25		19,699	10 - 600	68	50 +	60	M & F	0 - 9 rads	221/210=	1	0.08	8.3	0.0	26.0	
															1.05	5	0.05	5.3	0.0	16.7	RBE for n taken as 5, γ as 1.
A-bomb H + N 1945	2	γ + n	<10"	25	25	15 - 25		177,055	10 - 600	86	10 +	35	M & F	0 - 9 rads	615/544=	1	0.15	4.7	2.2	7.3	
															1.1	5	0.10	3.0	1.4	4.7	RBE for n taken as 5, γ as 1.

[a] This table does not provide a complete compendium of all studies; see text for selection. See Appendix VI for definitions of headings.

Table h-2

Basis of Risk Estimates for all Cancer Except Leukemia

Study population	Reference	Type of radiation	Duration of radiation exposure	Duration of follow-up (years)		Period after irrad. on which risk estimates are based (years)	Number of subjects	Number of person-years	Dose (rads)		Age at irradiation (years)		Sex	Nature of control	Relative risk (O/E)	RBE	Percent increase in relative risk per rem	Absolute risk, deaths or cases/10^6/year/rem			Footnotes or other comments
				Range	Mean				Range, External	Mean, to tissue	Range	Mean						Best	Limits		
																			Lower 90%	Higher 90%	
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)	(13)	(14)	(15)	(16)	(17)	(18)	(19)	(20)		(21)
Spondylitis Patients 1935-54	3	X	days to years	5-27	11	9-27	14,554	52,069	250-2,750	250	15-55+	36	M & F	England and Wales	$\frac{630.8}{284.6}$ = 2.2	1	0.49	7.3	5.2	9.4	84% male
										500							0.24	3.6	2.6	4.7	See footnote (b)

[a] This table does not provide a complete compendium of all studies; see text for selection. See Appendix VI for definitions of headings.

[b] From the reported data, a recalculation has been done to show the experience projected to the situation of all patients being followed for the longest interval, 27 years, and it is these recalculations that are used here. The numbers for observed and expected cases were derived from Table VI (ref. 4) by extrapolating the given data to the hypothetical case of a cohort of 10,000 people being followed from 9 to 27 years after irradiation. Thus, the calculation is as follows:

$$\text{Observed deaths} = \left(67 \times \frac{10,000}{27,082} \times 3 \right) + \left(46 \times \frac{10,000}{15,221} \times 3 \right) + \left(35 \times \frac{10,000}{9,766} \times 13 \right) = 630.8$$

$$\text{Expected deaths} = \left(32.52 \times \frac{10,000}{27,082} \times 3 \right) + \left(20.29 \times \frac{10,000}{15,221} \times 3 \right) + \left(15.67 \times \frac{10,000}{9,766} \times 13 \right) = 284.6$$

The number of person-years used to derive the absolute risk estimate is 190,000 (10,000 persons followed for 19 years). The error involved in not allowing for deaths during the hypothetical 19-year follow-up is so slight that it has not been corrected for in this calculation.

The estimate of the mean dose to the heavily irradiated organs has been assumed to be the same as that for the stomach. This dose has been estimated by the Committee to lie between 250 and 500 rads (see Appendix V). Since deaths from stomach and lung cancer make up 90% of the excess deaths due to cancer in the heavily irradiated sites and the estimated dose to the lung is 400 rads (see p. 196), this range of 250 to 500 rads for the mean dose to the heavily irradiated sites is reasonable. The line detailing the risk estimates has been divided in two, the upper and lower halves being based on a dose estimate of 250 and 500 rads respectively.

Table 2-1

Basis of Risk Estimates for Leukemia after Fetal Radiation

Study population	Reference	Type of radiation	Duration of radiation exposure	Duration of follow-up (years)		Period after irrad. on which risk estimates are based (years)	Number of subjects	Number of person-years	Dose (rads)		Age at irradiation		Sex	Nature of control	Relative risk (O/E)	RBE	Percent increase in relative risk per rem	Absolute risk, deaths or cases/ 10^6/year/rem		
				Range	Mean				Range, External	Mean, to tissue	Range	Mean						Best	Limits Lower 90%	Limits Higher 90%	Footnotes or other comments
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)	(13)	(14)	(15)	(16)	(17)	(18)	(19)	(20)		(21)
Fetuses England 1943-65	6 (7)	X	min.	-	-	0-10	-	-	0.5-2.0	0.8	0	0	M & F	-	1.63	1	79	27	23	32	see footnote (b)
Fetuses U.S. 1947-54	3	X	min.	6-10	8	0-10	C 77,000	C 616,000	0.5-2.0	1.0	0	0	M & F	fetuses not x rayed	1.54	1	54	27	12	41	
Fetuses A-bomb H + N 1945	20	γ + n	< 10"	10	10	0-10	715	7,150	1-500 +	50	0	0	M & F	Japan 1950-52	$\frac{0}{0.15} = 0.0$	1	0	0	0	5.9	Value of E calculated from 1950-52 vital statistics for Japan.

Table 2-1 (continued). Basis of Risk Estimates for Leukemia after Fetal Radiation[a]

Study population	Reference	Type of radiation	Duration of radiation exposure	Duration of follow-up (years)		Period after irrad. on which risk estimates are based (years)	Number of subjects	Number of person-years	Dose (rads)		Age at irradiation		Sex	Nature of control	Relative risk (O/E)	RBE	Percent increase in relative risk per rem	Absolute risk, deaths or cases/ 10^6/year/rem			Footnotes or other comments
				Range	Mean				Range, External	Mean, to tissue	Range	Mean						Best	Limits		
																			Lower 90%	Higher 90%	
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)	(13)	(14)	(15)	(16)	(17)	(18)	(19)	(20)		(21)
Fetuses England 1943-65	6 (7)	X	min.	-	-	0-10	-	-	0.5-2.0	0.8	0	0	M & F	-	1.62	1	78	30	24	37	See footnote (b)
Fetuses U.S. 1947-54	3	X	min.	6-10	8	0-10	C 77,000	C 616,000	0.5-2.0	1.0	0	0	M & F	Fetuses not x rayed	1.51	1	51	21	8	37	
Fetuses A-bomb H + N 1945	20	$\gamma + n$	< 10"	10	10	0-10	715	7,150	1-500 +	50	0	0	M & F	Japan 1950-52	$\frac{1}{0.21} = 4.8$	1	7.5	2.2	0	10	Value of E estimated from 1950-52 vital statistics for Japan

[a] This table does not provide a complete compendium of all studies; see text for selection. See Appendix VI for definitions of headings.

[b] This study was retrospective in design, and its use for risk estimation requires some modification in the basic tabular format. Leukemia cases and controls, and their subdivision as to fetal exposure to radiation from diagnostic x-ray examinations given to the mother are as follows:

	English series (Stewart) fetal radiation		
	+	-	Total
Leukemia cases	458	2,489	2,947
Controls	645	5,702	6,347
Total	1,103	8,191	9,294
Relative Risk			1.63

The proportionate increase in relative risk has been multiplied by normal mortality from leukemia at ages 0-9 (35 deaths /10^6/year) to yield an absolute risk estimate. The confidence limits on the absolute risk estimates were obtained from the parallel confidence limits on the relative risk estimate, the latter being calculated by the method of Woolf (Woolf, B. On Estimating the Relation Between Blood Group and Disease, Ann. Human Genet. 19:251-253, 1954) as modified by Haldane (Haldane, J.B. The Estimation and Significance of the Logarithm of a Ratio of Frequencies, Ann. Human Genet 20:309-311, 1955).

to 10 years of age) in the study of Stewart et al. A possible reason for at least part of the discrepancy between the two studies might be in the methodology used: Stewart et al. *(2)* relied in the main on mothers' memories whereas MacMahon *(3)* used hospital records for the source of the data. It is conceivable that if the mothers whose children died of cancer were more efficient in remembering whether they had diagnostic irradiation than the control mothers, this discrepancy would increase, the longer the interval between the pregnancy and the death of the child. In other words, the relative risk estimate would increase due to this systematic error, the older was the child at death. Until evidence is conclusive, it is prudent to assume that the latent period is effectively zero years and that the period of risk is at least 10 years in duration.

Equal Induction of Each Form of Childhood Cancer and Interpretation of the Data

In 1968 Stewart and Kneale *(7)* published a further report on their data, which showed that each of six categories of childhood neoplasia was equally induced by maternal abdominal exposure to x ray during pregnancy (Table II of their paper). The classes of neoplasia involved (leukemia, lymphoma, neuroblastoma, cerebral tumors, Wilms' tumor and all other cancer) differ markedly from one another with respect to epidemiologic characteristics *(8)*; hence the plausibility that low-dose intrauterine irradiation would increase the frequency of each by about 50% was questioned by Miller *(9)*. Establishment of a causal relationship would have been aided by showing a specificity of effect (for one rather than all forms of childhood cancer), and a consistency with data from animal or other laboratory experimentation. Interpretation of the results seemed further complicated by a previous report by a group of U.S. epidemiologists *(10)* who found in a collaborative (Tri-state) study conducted in Baltimore, Minneapolis, and New York State excluding New York City, that a similar (60%) excess of leukemia occurred in children whose mothers reported diagnostic x-ray exposures up to 10 or more years before conception of the children. Half as great an increase (30%), of borderline significance, was also observed with respect to paternal diagnostic irradiation before conception of the child. One must conclude that such an effect, if real, was heritable; however, it seems unlikely to be due to a genetic influence since a comprehensive study involving six indicators of genetic damage in the F_1 generation in Hiroshima and Nagasaki showed no detectable influence of radiation exposure (*11, 12*). Also, no excess of leukemia was observed in the F_1 generation (*13*) although the radiation dose-range was much greater than in the diagnostic x-ray studies. In addition, cytogenetic studies of atomic-bomb survivors in Japan showed complex chromosomal abnormalities if exposure occurred *in utero* or in later life, but not in the F_1 generation (conceived after the explosions) (*9, 14-17*). Thus, the claim that a preconception radiation is leukemogenic cannot now be linked to a genetic mechanism or chromosomal abnormality such as that which characterizes persons known to be at high risk of leukemia (*18*).

The authors of the Tri-state study, upon further examination of their data on preconceptional exposures, concluded that other factors interacted with radiation to increase the risk of leukemia appearing at 1-4 years of age *(19)*. Thus, for example, the relative risk rose about four-fold when such irradiation occurred in conjunction with a maternal history of miscarriages or stillbirths when, *and* in addition, the child had at least one viral infection more than 12 months before the onset of leukemia. The numbers of cases involved in this particular estimate, however, were very small. Statistical significance at the 5% level was attained when two radiologic factors (preconception *and* intrauterine exposures) were related to one or two pathologic factors (childhood virus infection or maternal miscarriages and stillbirths), or when one radiologic factor was related to both pathologic factors. Surely, as the investigators themselves said, these observations require confirmation (which will not come easily because of the massive effort required to collect such data). A further report from the Tri-state study by Bross and Natarajan (in press) finds that the relative risk of leukemia induction from previous diagnostic x rays to the mother during pregnancy is higher among children prone to allergy and some other diseases than among children whose immune and repair mechanisms, apparently, are in better order *(22)*.

As stated earlier, the finding that preconceptional irradiation is associated with an excess of childhood leukemia complicates interpretation of cancer occurrence following small intrauterine doses of x rays. It is difficult to rationalize why such similar results should occur whether exposure was prior to conception, as found in one well-executed study, or intrauterine—and if the latter, whether the outcome observed was leukemia or any other childhood cancer.

Linear Dose-Response Relationship

Stewart and Kneale *(20)* subsequently described a linear relationship between radiation dose (0.5+ abdominal films) and the excess in cancer risk under 10 years of age. The authors estimated that "among one million children exposed shortly before birth to one rad of ionizing radiations there would be an extra 300-800 deaths before ten years of age due to radiation-induced cancer (mean 572 deaths, standard error 133)." This estimated number of extra cancers per million rad of intrauterine exposure could be tested in another situation: the survivors of Hiroshima and Nagasaki. A study, recently reported by Jablon and Kato *(21)*, concerned 1250 children exposed *in utero* to less than 500 rad. The accumulated dose was 34,933 person-rad. Under the conservative assumption that half of the dose was attenuated by the mothers' bodies, 18.4 extra cancer deaths under 10 years of age would have been expected according to the Stewart and Kneale estimate (lower limit= 5.2), whereas essentially no extra cancer deaths were observed among the children exposed *in utero* to the atomic bombs. To explain the lack of agreement between the two studies, Jablon and Kato suggested that Stewart and Kneale may have overestimated the cancer induction rate; that the dose-response curve may be linear at low doses and concave downward at higher ones, as might occur if abortions were induced by radiation, i.e., a competing risk; that high energy atomic radiation may be a less effective carcinogen than is low energy x ray as used for diagnosis; or that factors other than x ray distinguish the irradiated from the nonirradiated fetus; i.e., low-dose x-ray exposure is not the cause of the childhood cancer, and the diagnostic procedure merely indicates that the pregnancy differed from normal. Another possibility is that the Japanese have a lower sensitivity to fetal irradiation than do Caucasians.

Conclusion

The studies reported to date indicate that diagnostic exposures during fetal life are associated with an increase in cancer deaths under 10 years of age. Whether or not radiation is causally related to the increase in cancer is open to question, since neither laboratory research nor clinical observations as yet support the concept that very low doses of irradiation might increase the relative frequencies of all categories of childhood cancer by about 50%. In any event, it is difficult to extrapolate from childhood cancers to adult cancers because of differences in type and epidemiology—and hence possibly in etiology.

The risk of childhood leukemia has been reported to be similar whether diagnostic x irradiation occurred during pregnancy or, in the only such study reported to date, as long as 10 years before conception. Study of the F_1 generation of Japanese survivors, however, has failed thus far to show an excess of leukemia following preconceptional irradiation. Also, comprehensive studies of the F_1 generation, using six indicators of genetic damage, have failed to reveal an effect. Hence, the interpretation of those studies which have reported an association between leukemia and preconceptional irradiation remains uncertain.

Despite uncertainty about the oncogenic effects of intrauterine exposures, we presume for purposes of conservative overall risk evaluation that such exposures do increase the risk of cancer in the child until 10 years of age but not thereafter.

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3. Total Cancer Risk

In view of variations among the different types of cancer in their relative rate of induction by irradiation (see Table 2., Appendix III), which are apparently unrelated to variations in the respective natural incidence levels, there is no basis for assuming that the incidence of all types of cancer will be increased by the same magnitude, in either absolute or relative terms, in response to a given dose. Hence estimates of overall cancer risk must be based either on direct observation of overall radiation-induced cancer excess, which as yet are incomplete due to the limited duration of follow-up of exposed populations, or on the total of the excess rates of different types of cancer, data for which are also incomplete at present.

In the atomic bomb survivors, the cumulative excess of all forms of cancer, including leukemia, corresponds to 50 to 78[1] deaths per 10^6 exposed persons per rem during the 20 year period from 1950-1970; i.e., from 5 to 25 years after exposure *(1)*.

Stewart *(2)* has raised a question concerning the general applicability of the ABCC results to radiation effects in man, arguing that observations of mortality were not made during the first five years after the bombings (prior to October 1950) and cites Bennet's report on the Bristol floods of 1968 (*3*) as evidence that a disaster may increase the number of cancer deaths in the year immediately following, presumably with a consequent lowering of cancer mortality in subsequent years. Jablon *(4)* has argued in rebuttal that even if such a disaster effect be conceded, the number of deaths involved would be too small to be apparent in a follow-up extending over a twenty year period from the fifth to twenty-five years after the bombings. This Subcommittee concludes that although some effect of the kind suggested by Stewart may be present in the ABCC data it would, at worst, be quantitatively very small and would have no practical effect on the risk estimates derived from the ABCC data.

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[1] This range is the result of assuming an RBE for the neutron component at Hiroshima of 1 to 5.

In patients treated with fractionated x-ray exposures for ankylosing spondylitis *(5)*, the excess mortality corresponds to a cumulative total of 92 to 165[2] deaths from cancer per 10^6 persons per rem during the 27 years immediately following irradiation.

If rates of radiation-induced cancer mortality similar to those above are assumed to apply generally and at the low dose levels approaching natural background radiation, then continual exposure of the U.S. population to a dose of 0.1 rem per year (approximately equivalent to natural background radiation) would be expected ultimately to cause approximately 1,350 - 3,300 cancer deaths per year, provided that the risk attributable to radiation did not persist for more than 27 years after any given increment of exposure. However, since the radiation-induced excess for many types of cancer is likely to persist longer than this period, as well as the fact that this simple calculation ignores other cogent variables, a somewhat more detailed approach has also been used to estimate the exccess cancer deaths in the U. S. population from continuous exposure to 0.1 rem/year. This approach, together with the various assumptions used, are outlined in full on the following pages. Such calculations must remain highly tentative in the absence of more complete data, but represent the best estimates that can be made at present. The numbers yielded by these calculations overlap those presented above, i.e., 2,000 to 9,000 annual cancer deaths in the U.S. population from 0.1 rem per year (Table 3-1). The wide spread in these estimates arises from our lack of knowledge of the long term consequences of irradiation of young children. According to the A-bomb data, these individuals appear to have a very high relative sensitivity (but a low absolute sensitivity) to cancer induction. Thus, if relative rather than absolute sensitivity is the appropriate way of determining risk *and* the risk is maintained throughout life, the upper figure of 9,000 annual extra cancer deaths in the U.S. population exposed to 0.1 rem/year is predicted from the relative risk model. With this limitation in mind, the Committee considers the most likely value to be approximately 3,000-4,000 cancer deaths (or a 1% increase in the spontaneous rate).

These figures must not be taken to represent more than crude estimates of risk, based on the incomplete nature of the data at present available. Several factors, not taken into account in the calculation of these estimates, exist which compound the uncertainty of these numbers. First, no allowance has been made for the liklihood that the carcinogenic effectiveness of low-LET radiation is reduced at low dose rates through the action of biological repair processes. Second, the individual cancer risks used in the derivation of the numbers may rise or fall as the follow-up of the study groups is extended to longer periods. Third, the risks have been derived for the most part at high total doses, which may have been sufficient to kill a large proportion of the normal or susceptible cells from which a cancer might result. Finally, the risk estimates themselves are crude and often have wide statistical confidence limits which are made even wider than is indicated in the tables by uncertainty about the dose-effect relation and the RBE values that must be used for neutron and alpha radiation for some of the exposed groups.

One further consideration is that these numbers reflect mortality data and do not, therefore, represent the number of individuals affected. If expressed in terms of incidence, including nonfatal cancers, estimates of risk could be higher by a factor of roughly 2. In addition to this, it can be calculated, using the relative risk model, that roughly 2,000-4,000 cases per year of thyroid cancer will be produced in the U. S. population from continuous exposure to 0.1 rem/year, using a 5-year latent period and either a 30-year or a lifetime plateau region.

Detailed examination of the table summarizing the calculations of the excess deaths in the U.S. population (Table 3-1) reveals the following:

1. When the absolute risk model is used, there is a small difference between the two assumptions of either a 30 year plateau (a) or

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[2] This range is the result of the lack of certainty in the dose to the heavily irradiated sites of these patients. The dose estimate used in this report is 250 and 500 rads (see Appendix V) and the dose to the spinal marrow has been taken at 880 rads. Part of the difference between this range of values and that given above for the ABCC experience might be due to the fact that a skin dose was used in the ABCC analysis and would be subject to appreciable attenuation, as mentioned earlier.

Table 3-1

Estimated numbers of deaths per year in the U. S. population attributable to continual exposure at a rate of 0.1 rem per year, based on mortality from leukemia and from all other malignancies combined.

Irradiation During Period	ABSOLUTE RISK MODEL[a]		RELATIVE RISK MODEL[a]	
	Excess Deaths Due to:		Excess Deaths Due to:	
	Leukemia	All other Cancer	Leukemia	All other Cancer
In Utero	75	75	56	56
0-9 years	164	(a) 73 (b) 122	93	(a) 715 (b) 5,869
10 + years	277	(a)1,062 (b)1,288	589	(a) 1,665 (b) 2,415
Subtotal	516	(a)1,210 (b)1,485	738	(a) 2,436 (b) 8,340
TOTAL	(a) 1,726 = 0.6% incr. (b) 2,001 = 0.6% incr.		(a) 3,174 - 1.0% incr. (b) 9,078 - 2.9% incr.	

[a] The figures shown are based on the following assumptions:

(1) 1967 U.S. vital statistics can be used for age specific death rates from leukemia and all other cancer, and for total U.S. population

(2) Values for the duration (a or b) of the latent period (the length of time after irradiation befor any excess of cancer deaths occur), duration of risk ("plateau region"), and magnitude of average increase in annual mortality for each group are as shown in Table 3-2.

a lifetime plateau (b) when applied to all cancers other than leukemia. Each assumption yields a calculated excess number of deaths of approximately 2,000, with leukemia deaths constituting about one fourth of the total.

2. Contrary to the absolute risk model, the relative risk model generates quite different numbers (by a factor of about 3) for the two assumptions (a) and (b) of the length of the plateau region for all cancers excluding leukemia. Examination of Table 3-1 reveals that almost the entire difference is due to the deaths generated from those irradiated when 0-9 years of age. It is caused by the assumed high relative risk (a 2% increase per rem) of cancer induction in this young age group being projected onto the over 50 year age group when the spontaneous cancer death rate is very high (see Table 3-3). No data are available as yet to test whether this assumption is true or false.

3. Agreement between the absolute and relative risk models is reasonably close except for the calculated excess of all other cancers arising from the age group 0-9 years at the time of irradiation. The reason for the high numbers generated by the relative risk model for this case is discussed in the preceeding paragraph. Other differences are due either to the fact that no attempt was made to produce absolute internal consistency between the relative and absolute risk estimates (e.g., the 2% increase per rad for leukemia induction in the 10 + yr. olds represents an absolute risk estimate of 1.6/10^6/year/rem in the U.S. population, not 1.0), or to the fact that the relative risk model tends to give somewhat higher numbers as the plateau region is projected into older age groups.

4. If the projections of these models are to be used for individuals occupationally exposed to radiation it is important to note that only the risk estimates for the "10 + year olds" will be relevant. The table below summarizes the projections of the two models assuming exposure beginning at 20 years of age and ending at 65, first in terms of excess deaths in the U.S. population to 0.1 rem/year, and second in terms of the excess deaths from cancer per million people assuming exposure to 5 rem/year (the current standard for occupational exposure). This latter expression of the risk incorporates the assumption that the million people have an age and sex distribution identical to that of individuals 20 years and older in the U.S. population (1967 statistics). Thus, the risk is obtained from the U.S. population figure by simple division by the number of people over 20 years of age (in millions) and multiplication by 50 (to convert from 0.1 rem/year to 5 rems/year). The figures do not represent an individual's chance of eventually dying from a radiation-induced cancer.

Calculation of the excess annual number of cancer deaths for individuals exposed from 20 to 65 years of age.

Exposure Conditions	ABSOLUTE RISK MODEL		RELATIVE RISK MODEL	
	Excess Deaths Due to:		Excess Deaths Due to:	
	Leukemia	All other Cancer	Leukemia	All other Cancer
U.S. Pop'n 0.1 rem/yr	195	(a) 721 (b) 808	436	(a) 1,444 (b) 1,793
10^6 people: 5 rem/yr.	81	(a) 300 (b) 336	181	(a) 601 (b) 746

Table 3-2

Assumed values used in calculating estimates of risk shown in Table 3-1.

Age at Irradiation	Type of Cancer	Duration of Latent Period (years)	Duration of Plateau Region (years)[a]	Risk Estimate	
				Absolute Risk[b] (deaths/10^6/yr/rem)	Relative Risk (% incr. in deaths/rem)
In Utero	Leukemia	0	10	25	50
	All other cancer	0	10	25	50
0-9 Years	Leukemia	2	25	2.0	5.0
	All other cancer	15	(a)30 (b)Life	1.0	2.0
10 + Years	Leukemia	2	25	1.0	2.0
	All other cancer	15	(a)30 (b)Life	5.0	0.2

[a] Plateau region = interval following latent period during which risk remains elevated.

[b] The absolute risk for those aged 10 or more at the time of irradiation for all cancer excluding leukemia can be broken down into the respective sites as follows:

Type of Cancer	Deaths/10^6/year/rem
Breast	1.5*
Lung	1.3
GI incl. Stomach	1.0
Bone	0.2
All other cancer	1.0
Total	5.0

* This is derived from the value of 6.0 quoted in Appendix II, Section A 1 e corrected for a 50% cure rate and the inclusion of males as well as females in the population.

Table 3-3

Calculation of the annual number of excess cancer deaths in the U.S. population from continuous exposure to 0.1 rem/year, using Relative Risk Model.

	From 1967 U.S. Vital Statistics		LEUKEMIA					ALL OTHER MALIGNANCIES								
			% Increase Due To Irrad'n During Period					% Increase Due To Irrad'n During Period								
Age	No. of Leuk. Deaths	No. of Ca Excl. Leuk Deaths	In Utero	0-9 yr	10 + yr	Total % Increase	Excess No. of Deaths	In Utero	0-9 yr (a)	0-9 yr (b)	10 + yr (a)	10 + yr (b)	Total % Increase (a)	Total % Increase (b)	Excess No. of Deaths (a)	Excess No. of Deaths (b)
0-4	684	795	3.75	0.45	-	4.2	29	3.75	-	-	-	-	3.75	3.75	30	30
5-9	801	699	3.75	2.75	-	6.5	52	3.75	-	-	-	-	3.75	3.75	26	26
10-14	478	733	-	4.8	0.2	5.0	24	-	-	-	-	-	-	-	-	-
15-19	411	929	-	5.0	1.1	6.1	25	-	0.5	0.5	-	-	0.5	0.5	5	5
20-24	264	1,059	-	5.0	2.1	7.1	19	-	1.5	1.5	-	-	1.5	1.5	16	16
25-29	222	1,321	-	3.75	3.1	6.8	15	-	2.0	2.0	0.05	0.05	2.05	2.05	27	27
30-34	233	2,226	-	1.27	4.1	5.4	13	-	2.0	2.0	0.15	0.15	2.15	2.15	48	48
35-39	312	4,532	-	-	4.9	4.9	15	-	2.0	2.0	0.25	0.25	2.25	2.25	102	102
40-44	438	9,102	-	-	5.0	5.0	22	-	2.0	2.0	0.35	0.35	2.35	2.35	214	214
45-49	588	15,525	-	-	5.0	5.0	29	-	1.5	2.0	0.45	0.45	1.95	2.45	303	380
50-54	726	23,688	-	-	5.0	5.0	36	-	0.5	2.0	0.55	0.55	1.05	2.55	249	604
55-59	935	32,022	-	-	5.0	5.0	47	-	-	2.0	0.60	0.65	0.60	2.65	192	849
60-64	1,223	38,284	-	-	5.0	5.0	61	-	-	2.0	0.60	0.75	0.60	2.75	230	1,053
65-69	1,536	42,587	-	-	5.0	5.0	77	-	-	2.0	0.60	0.85	0.60	2.85	256	1,214
70-74	1,783	43,880	-	-	5.0	5.0	89	-	-	2.0	0.60	0.95	0.60	2.95	263	1,294
75-79	1,697	37,557	-	-	5.0	5.0	85	-	-	2.0	0.60	1.05	0.60	3.05	225	1,145
80-84	1,202	25,062	-	-	5.0	5.0	60	-	-	2.0	0.60	1.15	0.60	3.15	150	789
85-89	600	12,128	-	-	5.0	5.0	30	-	-	2.0	0.60	1.25	0.60	3.25	73	394
90-94	172	3,710	-	-	5.0	5.0	9	-	-	2.0	0.60	1.35	0.60	3.35	22	124
95-99	24	681	-	-	5.0	5.0	1	-	-	2.0	0.60	1.45	0.60	3.45	4	23
100 +	5	69	-	-	5.0	5.0	-	-	-	2.0	0.60	1.55	0.60	3.55	1	3
Total:	14,336	296,647	56	93	589	Total:	738	56	715	5,869	1,665	2,415		Total:	2,436	8,340

Table 3-4

Calculation of annual number of excess cancer deaths in the U.S. population from continuous exposure to 0.1 rem/year, using Absolute Risk Model.

Age	1967 U.S. Pop'n (millions)	LEUKEMIA				ALL OTHER MALIGNANCIES						
		Excess Deaths Due to Irrad'n in Period			Total Excess Deaths	Excess Deaths Due to Irradiation During					Total Excess Deaths (a)	Total Excess Deaths (b)
		In utero	0-9 yrs	10+ yrs		In Utero	0-9 yrs (a)	0-9 yrs (b)	10+ yrs (a)	10+ yrs (b)		
0-4	19.191	36	3	-	39	36	-	-	-	-	36	36
5-9	20.910	39	23	-	62	39	-	-	-	-	39	39
10-14	19.885	-	38	2	40	-	-	-	-	-	-	-
15-19	17.693	-	35	10	45	-	4	4	-	-	4	4
20-24	14.572	-	29	15	44	-	11	11	-	-	11	11
25-29	11.958	-	24	19	43	-	12	12	15	15	27	27
30-34	10.860	-	11	22	33	-	11	11	41	41	52	52
35-44	23.838	-	1	60	61	-	24	24	179	179	203	203
45-54	22.588	-	-	56	56	-	11	23	282	282	293	305
55-64	17.571	-	-	46	46	-	-	18	263	307	263	325
65-74	11.678	-	-	29	29	-	-	12	175	263	175	275
75-84	5.945	-	-	15	15	-	-	6	89	163	89	169
85 +	1.174	-	-	3	3	-	-	1	18	38	18	39
TOTAL	197.863	75	164	277	516	75	73	122	1,062	1,288	1,210	1,485

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B. Mortality From Causes of Death Other Than Cancer

1. Adult

Experimental work has shown that single, sublethal doses of whole body radiation, and various regimens of divided doses, shorten the life expectation of exposed rats, mice, dogs, and other animals, and efforts to determine cause of death have suggested that excess mortality is not confined to cancer but extends rather generally over the spectrum of disease normally observed in these animals (*1*). The increase usually seems to be proportional to dose (*1-3*). On the basis of such data, estimates have been made of a life-shortening effect not only at the comparatively high doses and dose-rates used in experimental work, but also at relatively low dose levels and for man; e.g., that life-expectation may be reduced by one to five days per roentgen (*4, 5*).

Information on man is comparatively sparse, and observations on dose and dose rate less adequate. Human data pertain to occupational exposure, diagnostic or therapeutic exposure, and the Japanese A-bomb survivors, and relate to a time during which mortality rates have been falling rapidly. There is now little doubt that human life can be, and has been, shortened by exposure to ionizing radiation, in that the evidence is clear that such exposure is leukemogenic and, more generally, carcinogenic. The issue here concerns the identification of other specific diseases caused by ionizing radiation, and the likelihood that there has been, or may be, a *nonspecific* life-shortening, i.e., a reduction in life expectation from diseases generally, not merely from malignant neoplasms. The great difficulty with the human data, of course, is that they derive not from experiments, but from diagnostic or therapeutic situations, or from occupational choices, the effects of which cannot surely be separated from the effects of ionizing radiation. The data on A-bomb survivors, furthermore, may not be entirely free of such confounding, since socio-economic characteristics were not distributed uniformly over each city and hence also over each dose level. Also whether the heavy acute mortality, and the widespread deprivation and disease associated with the disorganization of each city following the bombings, in any way modified the late effects of radiation, remains unknown.

By 1950, papers by March (*6*), Henshaw and Hawkins (*7*), Ulrich (*8*), and Dublin and Spiegelman (*9*), had clearly established that U. S. radiologists were at higher risk of death from leukemia than other physicians and than the general population.

Dublin and Spiegelman, reporting on the mortality of U. S. medical specialists during 1938-1942, noted that specialists generally had lower age-standardized mortality ratios (SMR) than non-specialists (0.78 vs. 1.10), with specialists in roentgenology and radiology occupying a relatively high position among specialists (SMR = 0.90, third highest in their list of 12 specialists). With only 95 deaths observed among radiologists, they found only leukemia to have a remarkably high incidence in these physicians, in comparison with other specialists. In 1955 Warren (*10*) observed that the average age at death was about five years lower for U. S. radiologists generally than for other physicians. Since this was true not only for all causes of death but also for each of the many other causes of death he examined, Warren argued for a non-specific life-shortening effect of radiation in man. Although Warren gave some consideration to the comparability of radiologists and other physicians as to age, his analysis included no adjustment for differences in age structure, and the finding was challenged (*29*) on the basis that the five-year differential might reflect no more than differences in age composition.

Stimulated by Warren's report, Court Brown and Doll (*11*) examined the mortality of 1,377

British radiologists initially resident in Britain or Eire or belonging to the Colonial or Armed Services, over the period 1897-1956. With 463 deaths observed and expectation variously estimated on the basis of the general population, men in Social Class I, and physicans generally, they were unable to find evidence of non-specific life-shortening, but did observe a significant excess of mortality from cancer among men entering the practice of radiology before 1921, when serious attention seems first to have been paid to protective measures. Deaths from other causes were not elevated in any of the comparisons made. Selter and Sartwell reported a similar but preliminary study in 1959 (*12*), comparing 869 U. S. radiologists with 1,170 pathologists and bacteriologists as to mortality at ages 35 to 79 over the interval 1905-1956. With 235 deaths observed among the radiologists, and 244 among the pathologists and bacteriologists, and with incomplete reporting of cause of death, they found leukemia deaths to be definitely increased among radiologists, and deaths from other forms of cancer suggestively increased for radiologists elected to membership in their professional society in the period 1905-1914. In 1965 these same authors (*13*) reported more fully on the influence of occupational exposure to radiation, comparing the mortality of members of the Radiological Society of North America with that of members of the American College of Physicians and the American Academy of Ophthalmology and Otolaryngology, 16,339 men in all, with 3,421 deaths observed in the interval 1935-1958. In an age-controlled analysis they found the mortality of radiologists higher than that of the other groups throughout the period of study, but especially in 1935-1944. Most significantly, their analysis by cause of death showed that radiologists, especially at ages 65-79, had higher death rates not only from cancer but also from cardiovascular-renal diseases and from all other causes combined. Relative to the mortality risk of members of the American Academy of Ophthalmology and Otolaryngology, mortality ratios for radiologists in 1935-1958 were 1.4 times expectation for all causes, 2.5 for leukemia, 1.6 for other forms of cancer, 1.2 for cardiovascular-renal diseases and 1.6 for all other causes. At ages 65-79 these ratios were 1.5 for all causes, 1.9 for leukemia, 1.5 for other forms of cancer, 1.4 for cardiovascular-renal diseases, and 2.0 for all other causes. In matched-pair analyses they found a relative mortality risk of 1.3 for radiologists entering the specialty in 1921-1939 and no excess among men entering thereafter. A decreased rate of mortality of radiologists in recent years, *vis a vis* the general population, has also been reported by Warren (*14*).

In 1965 Court-Brown and Doll (*15*) reported their 5-to-25 year mortality follow-up on 14,554 patients with ankylosing spondylitis treated by x rays during the period 1935-1954. They classified the 1,582 deaths observed into (a) those directly attributable to arthritis and other forms of rheumatism, excluding rheumatic fever, (b) those attributed to conditions known to be associated with ankylosing spondylitis, e.g., ulcerative colitis, (c) leukemia, aplastic anemia, and cancer of heavily irradiated sites, and (d) others considered to be unrelated to the underlying disease and cancer of lightly irradiated sites. Expected deaths were calculated from the corresponding national mortality rates for England and Wales. Deaths observed in Group D numbered 812 vs. 608 expected, a mortality ratio of 1.3. Court-Brown and Doll found it difficult to interpret this excess mortality from unrelated causes, but were reluctant to consider it evidence of nonspecific aging in view of the other possible explanations.

Miller and Jablon (*16*) recently reported an 18-year follow-up of 6,560 men who served as x-ray technologists in the U. S. Army during World War II, compared with 1,522 pharmacy and 5,304 medical technologists. With 289 deaths observed among the x-ray technicians, and 256 among the other two groups of technicians, they found only a questionable increase in bronchogenic carcinoma among the x-ray technicians, and no evidence of any general mortality increase. In his recent report on 3,239 Massachusetts dentists (*17*), most of whom received some exposure to radiation in their work, Warren found no evidence of excess mortality in comparison with U. S. white males of comparable age. Duncan and Howell, studying the experience of employees of the United Kingdom Atomic Energy Authority during the period 1962-1968 (*18*), when exposure averaged 0.3 man-rad/year, found no association between the working environment and morbidity, and fewer deaths than expected from the mortality rates of the general population of the same age and sex (*18*). Although the mortality comparison is based on 200,000 man-years of exposure, use of death rates of the general population seems inappropriate for an employed population. The morbidity data pertain to 69,000 man-years of observation during 1964-1968 and are internally controlled.

Tachikawa and Kato (*19*) have recently reported the mortality experience of Hiroshima A-bomb survivors ascertained by means of a Hiroshima City survey in August 1946. Mortality from 1 October 1946 to 1 October 1950 was highest for those closest to the hypocenter at the time of the bomb (ATB). However, only for leukemia and deaths of unknown cause was there any relationship with distance ATB. The cohort of 82,271 A-bomb victims under continuing mortality surveillance at the Atomic Bomb Casualty Commission (*20*) experienced 13,093 deaths from 1 October 1950 to the end of September 1966. These deaths have recently been analyzed by Beebe et al. (*21*) in relation to the revised (T-65) dose as well as to distance ATB, and with regard to about 50 cause-of-death groups. The hypothesis of accelerated aging was one of many considered in this analysis. Apart from the excess mortality observed for leukemia and for diseases of the blood and blood-forming organs throughout the 16-year period, and for forms of cancer other than leukemia, especially in the 1962-1966 interval, systematic mortality differentials associated with distance or dose were not seen. Jablon and Kato have re-examined this material (*28*) and extended the period of observation through 1970. In the six-year period, 1965-1970, they find no more than suggestive evidence (P = 0.06) of an increase in mortality from all the diseases except neoplasms among A-bomb survivors exposed to more than 100 rads. The suggestion rests on an estimated excess of 24 deaths above the expected 218. Their analysis by age and by disease-groups and systems throws no further light on the source of the possible discrepancey.

Thus far the experience of the A-bomb survivors does not confirm the hypothesis of accelerated aging, but it remains possible that the youngest victims of the bombs will eventually show a disturbance of mortality patterns consistent with the hypothesis of accelerated aging. By 1970 those under age 10 ATB were under 36 years of age. The mortality differences seen thus far seem better explained in terms of more specific relationship between ionizing radiation and individual diseases or groups of diseases, especially the leukemias, other malignant neoplasms, and diseases of blood and blood-forming organs.

The argument for a nonspecific aging effect of radiation in man rests on an extrapolation from animal data, and on inferences from comparisons of occupational groups and patient-groups which are open to the possible influence of other factors, notably those associated with occupational choice and with the diseases being treated by radiation. In contrast, the exposure of the Japanese in Hiroshima and Nagasaki is relatively free from such influences, but only relatively because socio-economic characteristics are not uniformly distributed over each city and hence also over all dose levels. It differs also in having been a single, whole-body dose ranging from the neighborhood of 0 at several km from hypocenter to supralethal amounts in the vicinity of the hypocenter. Immediate mortality from the bombs exceeded 50 percent at about 1.25 km in Hiroshima and 1.35 km in Nagasaki (*22*); 20 percent mortality, in turn, corresponds to about 1.75 km in Hiroshima and 1.80 km in Nagasaki. Whether the initial mortality was selective in the sense that survivors would be less vulnerable to late chronic effects remains unknown. Nor is the evidence drawn from occupational and patient-group comparisons uniformly suggestive of the existence of a nonspecific aging effect. The hypothesis remains unproved but the evidence in its favor is strong enough to require further investigation.

The age-adjusted data on U. S. radiologists (*13, 29*) have not been reported in great detail by cause, but a relative risk estimate of 1.2 is given for cardiovascular-renal diseases, and mortality from these causes is also elevated among the patients with ankylosing spondylitis compared with national death rates. These diseases have been intensively studied at ABCC on the basis of both clinical and autopsy observations (*23-26*), with no suggestion of a radiation effect ever having been seen. It should be noted, however, that some of the specific diseases included in the cardiovascular-renal complex have very different mortality rates in Japan in comparison with the U. S. (*27*). Apart from cancer and the cardiovascular-renal diseases, it is only for diseases of blood and blood-forming organs that impressive differentials in mortality have been associated with radiation (*11, 21*) but it seems likely that this is no more than a small part of the leukemogenic effect, misclassified.

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2. *Infant Mortality and Ionizing Radiation*

In 1954, Yamazaki et al. (*1*) reported increased rates of fetal death and of infant mortality among children who were *in utero* at the time of the atomic bombing of Nagasaki. They divided the population into three subgroups: (a) 30 fetuses whose mothers were exposed within 2000 meters and had signs of major radiation injury, (b) 68 whose mothers were exposed within 2000 meters without evidence of radiation injury, and (c) 133 "controls" whose mothers were between 4000 and 5000 meters distant from the hypocenter. In these three groups there were, respectively, 7 (23%), 3 (4%) and 3 (3%) fetal deaths. Among livebirths in the three groups, there were, respectively, 6 (26%), 3 (5%), and 4 (4%) neonatal and infant deaths. The numbers are, of course, very small. In addition, as the authors pointed out, it is difficult to interpret the high fetal and infant loss rates in the heavily exposed group since factors other than radiation, such as trauma, burns, infections, etc., may have played a role.

A substantially larger series, encompassing the data both from Hiroshima and Nagaski, has been reported recently by Kato (*2*). The distribution of exposed fetuses by estimated maternal dose received, and the observed and expected infant deaths (the expected being based on the death rates in the group as a whole, standardized for sex and trimester of exposure) are as follows:

Estimated maternal dose (rads)	0-9	10-39	40-79	80+	Unknown	TOTAL
Infants exposed *in utero*	795	223	180	68	26	1292
Infant deaths: Obs.	60	11	19	13	1	104
(<1 year) Exp.	62.9	18.0	15.1	6.1	1.9	104.0
Observed/Expected	0.95	0.61	1.26	2.14	—	1.00

There is little doubt that the more heavily exposed infants experienced higher infant mortality rates than the lightly exposed. There are, however, some features of the data that suggest that factors other than radiation may have been responsible. Specifically, the increase in mortality was noted only for infants exposed in the third trimester of pregnancy, and there was a striking increase in the proportion of low birth weight infants in the highest exposure group (35% under 2500 meters, compared to 9% in the 0-9 rad group). Factors other than radiation operating in the third trimester could have affected birth weight possibly by induction of premature labor. Hence some of the concomitants of heavy exposure other than the radiation *per se* require further investigation before a judgment can be made as to the role of irradiation in the observed excess of mortality *(3)*.

A genetic mechanism for association between environmental radiation levels and infant mortality has been proposed recently by Sternglass (*4*). The evidence presented to support this hypothesis consists of temporal and geographic correlations of infant mortality rates with levels of radioactive fallout from atomic weapons testing or from nuclear power installations. In addition, experimental data on mice are cited as evidence that genetic effects of strontium-90 have been observed. That the mechanism of increased infant mortality associated with increase in environmental radiation is genetic, rather than somatic, is deduced from a lag of five years between the fallout from the first weapons test in New Mexico in 1945 and appearance of the increased mortality.

The evidence assembled by Sternglass has been critically reviewed by Lindop and Rotblat (*5*) and by Tompkins and Brown (*6*). It is clear that the correlations presented in support of the hypothesis depend on arbitrary selection of data supporting the hypothesis and the ignoring of those that do not. In several regards, the data used by Sternglass appear to be in error. One of the most vital assumptions in the model —that without the atomic tests the infant mortality rate would have continued to fall in a geometrically linear fashion—is without basis either in theory or in observation of trends in other countries and other times. The doses of strontium-90 used in the experiments referred to by Sternglass were of the order of 100,000 times greater than those received by humans from all the atomic tests and were associated with extremely small differences in infant mortality (8.7% in the irradiated vs. 7.5% in the control mice) *(5)*.

In short, there is at the present time no convincing evidence that the low levels of radiation in question are associated with increased risk of mortality in infancy. Hence, for the purposes of this report, no estimate of risks are considered to be applicable.

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C. Morbidity from Causes Other Than Cancer

1. Cataracts

Although it is generally accepted that the human lens is sensitive to opacification by fast neutrons, the dose-response relation for induction of cataracts severe enough to impair vision seems clearly to be sigmoid, at least for low-LET radiation (*1*). In the case of x rays and gamma rays, the threshold varies from 200 to 500 rads, when delivered in a single brief exposure, to 1000 rads or more when delivered over a period of months (*1, 2*). For high-LET radiations, the data are fragmentary; however, observations suggest that there is a threshold for fission neutrons in the vicinity of 75-100 rads, which depends less on intensity than does the threshold for low-LET radiations (*1*).

Despite evidence for the existence of a threshold for opacities severe enough to impair vision, minute amounts of radiation (less than 5 rads) may suffice to cause microscopically detectable lens changes in radiosensitive species such as the mouse (*3, 4*). Whether corresponding changes might ultimately be elicited by comparable doses in the human lens after a suitably long latent period remains to be determined.

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2. Central Nervous System Effects

The central nervous system is relatively resistant to induction of structural changes by irradiation at dose levels below several hundred rems except early in its growth and development (*1*); however, it has been reported to show transitory functional changes in response to acute doses as low as 1 rem (*2*). It has not been demonstrated that these changes produce any injurious effects.

Effects on the developing nervous system are surveyed elsewhere in this report (see Chapter VI).

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3. Impairment of Fertility

Testis

Among the most radiosensitive cells of the body are primitive sperm precursors, the spermatogonia; by contrast, mature spermatozoa are relatively resistant to killing. Spermatogonia are drastically depleted by small amounts of radiation; i.e., a dose of 50 rem delivered in a single brief exposure may result in cessation of sperm formation. Fertility is not impaired, however, until the pre-existing sperm cells and those formed from the maturation of surviving spermatocytes and spermatids are eliminated from the genital tract, which takes several weeks (*1*). The sterility ensuing after such a dose may be expected to be only temporary, since enough spermatogonia survive to restore spermatogenesis through eventual regeneration of the seminiferous epithelium (*2*).

In men who have received testicular irradiation in criticality accidents or radiotherapy, the time required for the sperm count to return to normal has varied from about one year after a dose 100 rem to more than three years after near-lethal exposure (*2*). Because acute whole-body irradiation has not been observed to cause permanent sterility, the sterilizing dose for man, as for other male mammals, is thought to exceed the lethal dose if applied to the whole body in a single, brief exposure (*3*).

Protracted or fractionated whole-body irradiation, on the other hand, has caused permanent sterility in male laboratory animals, depending on the dose rate and quality of radiation (*4*). In dogs exposed daily to x radiation for the duration of life, no change in sperm count was detectable at or below a dose rate of 0.6 rem per week, whereas sterility occurred within months at a dose rate of 3.0 rem per week (*5*). It is conceivable, therefore, that permanent sterilization of the human testis might also result from protracted exposure, although such an effect has yet to be reported. In any event, it seems unlikely that impairment of fertility would occur at dose levels compatible with existing radiation protection standards (*6*).

Ovary

Unlike the testis, the ovary possesses its entire supply of germ cells, or oocytes, early in life and lacks the ability to replace them as they are lost subsequently. Hence, since oocytes are relatively radiosensitive, irradiation causes a lasting reduction in the reproductive potential of the affected ovary, varying in severity with species, age, and other factors (*7*).

Data on the response of the human ovary come chiefly from observations of the effects of therapeutic irradiation, from studies of Japanese atomic bomb survivors, and from investigation of Marshallese women exposed to fallout (*7*). The data suggest that a minimum of 300-400 rems must usually be given in a single exposure to insure permanent sterility and that an even larger dose (i.e., 1000-2000 rems) is required for sterilization if administered to young women in fractionated exposures over a period of 10-14 days (*6-7*). That ovarian sensitivity may vary, however, is implied by the suggestion that a single dose of 170 rems is "not without risk of permanent sterilization" in some young women, although the same total dose given in two or three weekly fractions may apparently increase fertility in others who have a history of infertility (*6*). Follow-up studies of Japanese atomic-bomb survivors and Marshallese women exposed to nuclear fallout have disclosed no lasting impairment of fecundity (*6*).

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Appendix III. Analysis of Viewpoints on Record

A. United Nations Reports

The United Nations Scientific Committee on the Effects of Atomic Radiation in its 1964 report (*1*) estimated the increased risk of radiation-induced leukemia to be one to two cases per million people exposed per rad per year. For thyroid cancer, the estimate was one case per rad per year per million. On the basis of the data then available, it was estimated that approximatley one other cancer (excluding thyroid) would occur for every leukemia induced by irradiation. The Committee cautioned that these estimates were reliable only for the dosage range where the data were reasonably good (above about 100 rads) but that extrapolation to low doses could be considered to give an upper limit to the risk. It was pointed out that the duration of the period of increased risk was not known and that since cancers other than leukemia might well have longer latent periods for their induction, the ratio of other cancers to leukemia might increase as the period of follow-up was extended. In both the 1962 (*2*) and 1964 (*1*) reports, the United Nations Committee emphasized that radiation delivered at low dose rates was probably much less effective than that given at high rates but that the data were inadequate to make a numerical estimate of the factor of change in effectiveness.

B. Reports of the International Commission on Radiological Protection

In 1965, a Task Group of the International Commission on Radiological Protection (ICRP) submitted a report to ICRP's Committee I on "The Evaluation of Risks from Radiation" (*3*). In essence, the estimates of risk of radiation-induced neoplasms were identical to those of the U. N. Committee. Using the linear, nonthreshold hypothesis, the Task Group estimated that if one million persons were exposed to one rad the total excess number of cancers over the lifetime of this population would be: 20 leukemias, 20 other cancers (except thyroid) and 10 to 30 thyroid cancers. They assumed the period of increased risk would extend from 10 to 20 years which, of course, makes their estimate correspond to 1 to 2 leukemias per million persons exposed per rad per year, etc. They indicated that there might subsequently be found an increased risk of other cancers (because of the longer latent period) but they considered it unlikely that the increase would reach a factor of ten. The Task Group considered these as upper limits of risk and pointed out that at very low doses and dose rates some of these effects might not occur at all.

The shortcomings and uncertainties in the risk estimates from the UN and ICRP committees were well recognized and discussed in detail in their reports. Both reports depended heavily on data from the Atomic Bomb Casualty Commission (ABCC) and from patients treated with radiation for ankylosing spondylitis. One of the uncertainties has been and will continue to be reduced with the passage of time, namely, the question of whether the ratio of other neoplasms to leukemia will increase as the follow-up progresses. The uncertainties concerning the effect of dose rate and the shape of the dose-response curve will require data for their resolution and the necessary data do not appear in the offing.

More recently, two Task Groups of Committee I of the ICRP have reported on "Radiosensitivity and Spatial Distribution of Dose" (*4*). The Group reporting on radiosensitivity attempted to estimate the order of sensitivity to cancer induction of the various organs and parts of the body. They were able to do this in a tentative way but pointed out that the data were adequate for risk estimates (slope of the assumed linear dose-response relationship) only for two tissues, namely, bone marrow and thyroid. They considered the lymph nodes and reticular tissue to have a high sensitivity but properly based risk estimates were not available. Other tissues that might have a high sensitivity included the pharynx, bronchus, pancreas, stomach, and large intestine, but the evidence was considered to be "incomplete or capable of other interpretations." A few organs (ovary, breast, prostate, uterus, bladder) were not classified, and the remaining tissues were believed to have a low sensitivity.

The question of the ratio of other cancers to leukemias was again considered and the Task Group on Spatial Distribution of Dose estimated that by 27 years after exposure to radiation this ratio might be as high as 5 or 6 to 1. This conclusion was based on data from Court Brown and Doll (5) on the spondylitics. The patients with the longest period of follow-up showed no evidence of a decrease in the excess incidence of "other cancers" whereas the period of high risk from leukemia appeared to end at about 14 years. Perhaps the principal criticism of this conclusion arises from the fact that the majority of the excess cancers originated in the bronchus or stomach. The Task Group on Radiosensitivity commented on the excess of these two types of cancer in the spondylitics as follows: ". . .the large quantities of drugs, especially analgesics, which spondylitics inevitably consume, may conceivably have a direct carcinogenic effect on the stomach or an indirect and synergestic action together with irradiation. Similarly, the change in respiratory dynamics associated with increased rigidity of the chest may increase the carcinogenicity of cigarette smoking and so make invalid the calculation from national statistics of the expected number of cases of bronchial carcinoma in the absence of irradiation. Similar reasoning might be used to explain away the excess of cancer of the pharynx. There are no data on unirradiated spondylitics which would allow these suggestions to be checked." It is pertinent to note that the combination of aminopyrine, an analgesic drug formerly in wide use, with sodium nitrite, a food additive used extensively, yields nitrosamine. The reaction takes place at pH values found in the stomach (*6*). Nitrosamines have been shown to be potent carcinogens in animals, yielding malignancies of the stomach and lung. The incidence of these cancers in the exposed patients was high. It would be of considerable importance to determine how many of the patients had, in fact, used aminopyrine.

C. Report by Dolphin and Marley

Dolphin and Marley (*7*), drawing on essentially the same data as the Task Groups of ICRP, provided risk estimates that were very similar to those of the Task Groups. They estimated the total risk of leukemia as 20 cases per 10^6 man-rads, and that the risk of thyroid cancer is 30 and 10 per 10^6 man-rads for children and adults, respectively. They noted that thyroid cancer is not usually fatal and suggested that for risk calculations only 10% should be considered as fatal. Dolphin and Marley also specifically recommended that these risk coefficients not be applied to dose levels below 10 rads.

D. Report by Mole

Mole (*8*) has pointed out that since the ratio of other cancers to leukemia will probably reach 4 or 5 to 1 in the spondylitics who received partial-body radiation the ratio might reach 10 to1 in persons receiving total body radiation. The view extends the conclusion of the ICRP Task Group Report (ICRP 14), which attempted to evaluate from independent sources the radiosensitivity of organs not included in the irradiation field in the case of spondylitis. The Task Group was unable to establish a high sensitivity except in the case of the thyroid gland.

E. Report by Baum

Despite the seemingly rather general acceptance of the linear hypothesis for protection purposes, there have been recent reports suggesting certain alternatives. For example, Baum (*9*) has elected to fit a power function to certain selected data, and from the slope constant he has sought to deduce whether the curve (on a linear plot) is convex, straight, or concave. The data for neoplasms in human populations that he used to illustrate the power function were all from studies of the ABCC. These included: all malignancies (Hiroshima), lung cancer (both cities), stomach cancer (both cities), breast cancer (both cities), acute leukemia (Nagasaki), and all leukemias (Hiroshima) (*10-16*). In every case, he found the exponent of the power function to be less than 1.0, implying a convex curve on a linear plot (greater effectiveness per rad at lower doses). Data for lung, stomach, and breast cancer are too fragmentary and the numbers of cases too small to justify the fitting of any regression equation (Miller (*10*), ICRP 14 (*4*)) to say nothing of choosing among alternatives.

F. Reports by Gofman and Tamplin

Estimates have been made that if the current FRC guidelines for the maximum "allowable" dose from all nonmedical sources of 0.17 rem per year to the general population is reached, some 32,000 extra deaths per year from all malignancies in the U. S. population will result (*17-19*). More recently, the same authors have refined their estimates, concluding that the additional cancer death rate may be as high as approximately 104,000 per year or an increase of 34.3% over the current rate (*20*). The basis for the estimates rest on three generalizations:

GENERALIZATION I

All forms of cancer, in all probability, can be increased by ionizing radiation, and the correct way to describe the phenomenon is either in terms of the dose required to double the spontaneous mortality rate for each cancer or, alternatively, of the increase in mortality rate of such cancers per rad of exposure.

GENERALIZATION II

All forms of cancer show closely similar doubling doses and closely similar percentage increases in cancer mortality rate per rad.

GENERALIZATION III

Youthful subjects require less radiation to increase the mortality rate by a specified fraction than do adults.

In addition to these three generalizations, two further assumptions are made, viz:

(i) The radiation dose-response curve is linear at all dose levels.

(ii) There is no dose-rate effect for any type of radiation-induced malignancy.

Analysis of certain data on radiation-induced neoplasia in the light of these assumptions enables the authors to construct the following table of the age-specific radiosensitivity of cancer induction (*20*).

Table III-1: Variation in Cancer Induction per rad (Table 4 of ref. 20)

Age at Irradiation	Increase in Cancer Mortality Rate per rad (in plateau region) (percent)
In utero	50
0-5 years	10
6-10	8
11-15	6
16-20	4
21-30	2
31-40	1
41-50	0.5
51-60	0.25
61 +	Assumed negligible

These relative risk estimates are then applied to the hypothetical case of exposure of the U. S. population to 0.17 rem/year using three models differing in the lengths of the latency period and plateau region. The most "pessimistic" case, which assumes latency periods of 5 and 15 years for in utero irradiation and all subsequent irradiation respectively, and a plateau region which never returns to the spontaneous rate, predicts an annual radiation-induced cancer mortality rate of 104,259 cases, or a 34.3% increase in the present rate. The most "optimistic" case, which assumes 5 and 10 year latency periods for in utero and all other irradiation, together with a plateau region of 20 years, predicts an increased cancer mortality rate of 9,428 cases or a 3.1% increase.

Careful analysis both of the data used by the authors in their generalizations and risk estimates and of other relevant studies has led to the following conclusions:

(a) The epidemiological studies of Stewart and Kneale (*21*) and of MacMahon (*22*) on the incidence of malignancy in offspring of mothers given diagnostic irradiation during pregnancy support generalizations I and II and also the risk estimate of a 50% increase in cancer mortality per rad for in utero irradiation. The fact that it cannot be proved conclusively that the diagnostic irradiation was the causative agent in producing the increased cancer mortality cannot be used to reject the data.

(b) The data of Court Brown and Doll (*23*) on the follow-up of patients treated in early adulthood for ankylosing spondylitis constitute a

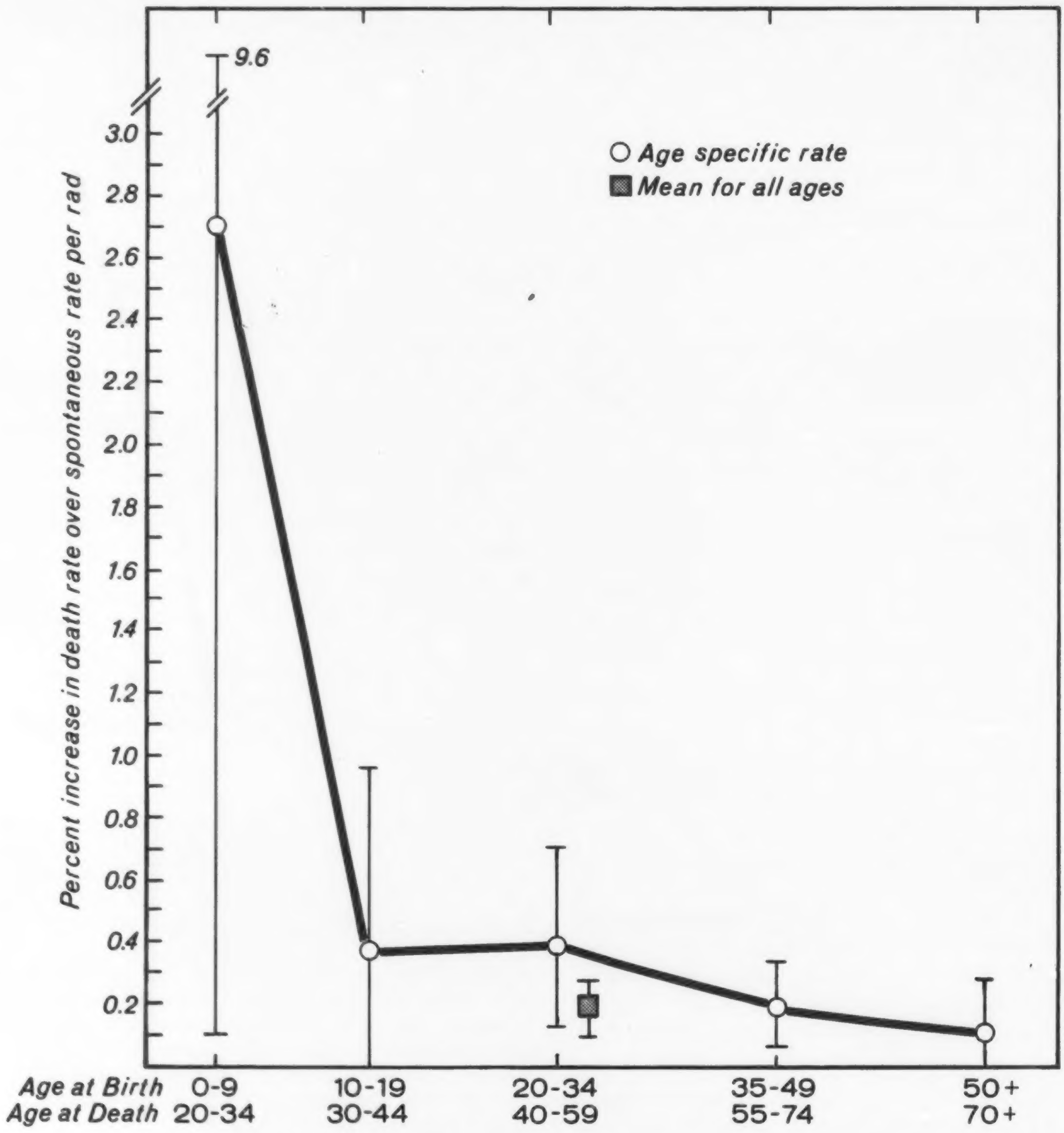

Figure III-1. The relative risk of induction of all malignancies (except leukemia) in the A-bomb survivors versus age at the time of the bomb (ATB). These data are for both cities and sexes combined for deaths between 1960 and 1970. No neutron RBE has been applied.

critical part of the evidence used in support of generalizations I and II. Basically, these two rules would predict that in a population receiving whole-body irradiation the ratio of the excess number of cancers to excess number of leukemias should be the same as the ratio of spontaneous rates experienced by a non-irradiated population. Since the spondylitics did not receive whole-body irradiation, a correction factor has to be applied to the so-called "heavily irradiated" sites to equalize their dose to that of the bone marrow (presumably the site of origin of the radiation-induced leukemias). This correction factor was obtained from estimates made by Dolphin and Eve (*24*) of the mean dose received by the stomach in the spondylitics. These authors stated that the mean stomach dose might well be only 0.07 of the mean dose to the spinal marrow. Applying this factor brings the stomach dose to 61.6 R compared with the estimated dose to the entire marrow of 352 R. This reasoning means that the ratio of excess stomach cancer deaths to excess leukemic deaths should be multiplied by $\frac{352}{61.6}$ (=5.71) to correct for the estimated difference in radiation dose. It is clear from the above that the estimation of the mean stomach dose from the mean dose to the spinal marrow is crucial. The committee has reconsidered this question and has concluded that the previous estimate made by Dolphin and Eve is seriously in error. A full discussion of this evaluation is given in Appendix V. It is sufficient to state here the conclusion, namely, that the *minimum* value of the mean dose to the stomach is 250 rads, and a value of double this is not unlikely. If it is assumed that this dose estimate applies to all "heavily irradiated" sites (as Gofman et al. assumed) then the percent increase in cancer mortality per rad becomes 0.2 to 0.4, or *a factor of 5 to 10 less than that predicted* (for persons aged 21-30).

(c) The most unequivocal data on the induction of neoplasms in humans comes from the ABCC studies. Analysis of the death certificate data up to 1970 reveals that the doubling dose for the induction of all malignancies (excluding leukemia) in those exposed when aged ten or more is at least 500 rads (Table h-2), representing a 0.2 percent increase per rad. Table III-1 shows that Gofman et al. (*20*) assumed a percent increase per rad varying from 6 for 11-15 year olds to 0.25 for 51-60 year olds. In calculating lifetime risk estimates, this sliding scale of relative sensitivity is equivalent to a constant value of at least 10 times higher than that derived from the most recent ABCC studies. Figure III-1 shows the ABCC data up to 1970 in terms of percent increase in the death rate from all malignancies except leukemia against age ATB.

(d) Analysis of the ABCC data shows that those survivors who were exposed when less than ten years old suffered a higher relative risk of developing a malignancy than did those who were older than ten at the time of the bomb. That is, in terms of relative risk, generalization III is correct; youthful subjects *do* require less radiation to increase the mortality rate from cancer by a specified fraction than do adults. However, the best estimate of the percent increase in cancer mortality per rad that can be made for all cancer except leukemia (Table h-1) shows that the values calculated by Gofman et al. (*20*) (shown in Table III-1) are overestimates of the risk by a factor of approximately 4.

(e) Doubling doses for induction of various different neoplasms in the Japanese survivors of the atomic bombs are not equal to each other as can be seen from Table III-2 below:

Table III-2: A comparison of relative and absolute risk estimates of the major types of malignancies induced among the A-bomb survivors (all ages).

Type of Neoplasm	Period of Observation[3]	Spontaneous Incidence[1]	Absolute Risk Est.[2]	Doubling Dose[2]
Lung Cancer	1955-70	17.8	0.85	215
Breast Cancer	1965-70	6.7	2.43	28

Table III-2: A comparison of relative and absolute risk estimates of the major types of malignancies induced among the A-bomb survivors (all ages)—continued

Type of Neoplasm	Period of Observation[3]	Spontaneous Incidence[1]	Absolute Risk Est.[2]	Doubling Dose[2]
All GI less Stomach Cancer	1960-70	61.8	0.76	813
Leukemia	1950-70	4.5	1.71	26

[1] Calculated from the rate in the 0-9 rads group and expressed in deaths/10^5/year.

[2] Estimates based on a comparison of the 0-9 rad with the 10 + rad group. The absolute risk estimate is in deaths/10^6/year/rad. No RBE correction for dose attenuation or for the RBE of neutrons has been applied.

[3] This is the period over which the rates of the respective cancers were found to be increased.

It is apparent from this comparison that the thesis that doubling doses for different types of cancer are roughly equal does not apply to the A-bomb survivors, at least as far as the data are at present available. If any general rule can be drawn from this small sample, it would be that the absolute risk estimates are roughly equal despite the very different spontaneous incidences of the different types of cancer. This conclusion, together with the lack of any suggestion of an excess number of cancers of the stomach, cervix and uterus, throws grave doubt on the validity of generalizations I and II when they are analyzed in terms of the data collected up to 1970 on the A-bomb survivors.

(f) Data on death of U. S. radiologists (*25*) from leukemia and all other cancer do not support the thesis that the relative risk of leukemia induction is the same as that for all other cancer. For example, the relative risk of leukemia death in the 50-79 age group of RSNA members compared with AAOO members is 2.9 (17 observed compared with 5.8 expected at AAOO rates), whereas for all other cancer deaths in the same age group the relative risk is 1.6 (126 observed compared with 79.6 expected). Unfortunately, these data can be analyzed only on a semi-quantitative basis due to a lack of detailed information on dosimetry and on the kinetics of development of the excess deaths in each case and also due to the possible unsuitability of the controls, but on this basis alone the data imply that the relative risk of leukemia induction is roughly 3 times greater than that for all cancer induction.

(g) Despite the above criticism, it is felt that it may be better in some cases to express risk in relative rather than absolute terms. This is due to the fact that a constant doubling dose for a particular neoplasm may be the best way to deal with changes in the spontaneous rate of that malignancy during adult life. This has been shown to be true for leukemia induction in spondylitics (*26*) and it also appears to be true for lung cancer in uranium miners in whom the effect of mining (radiation) is seen as a multiplication of the spontaneous incidence by a factor which is the same whether the miners were smokers or not (*27*). Whether or not this holds for the induction of solid tumors in the A-bomb survivors is a moot point as can be seen from Figure III-2. A constant absolute risk would yield a horizontal line, whereas a constant relative risk would yield a line parallel to the age specific cancer death rate curve. As can be seen from this figure neither prediction is strictly followed.

(h) More critical than the actual values of the risk estimates are the assumptions that have to be made on the lengths of the latency and plateau regions before any overall evaluation of risk can be made. Unfortunately, there are very few data on which to base realistic estimates of the lengths of these two periods. Analysis of the evidence that does exist suggests that the most likely estimates are as follows:

(i) Irradiation in utero: a latency of zero years and a plateau region of 10 years for all malignancies including leukemia.

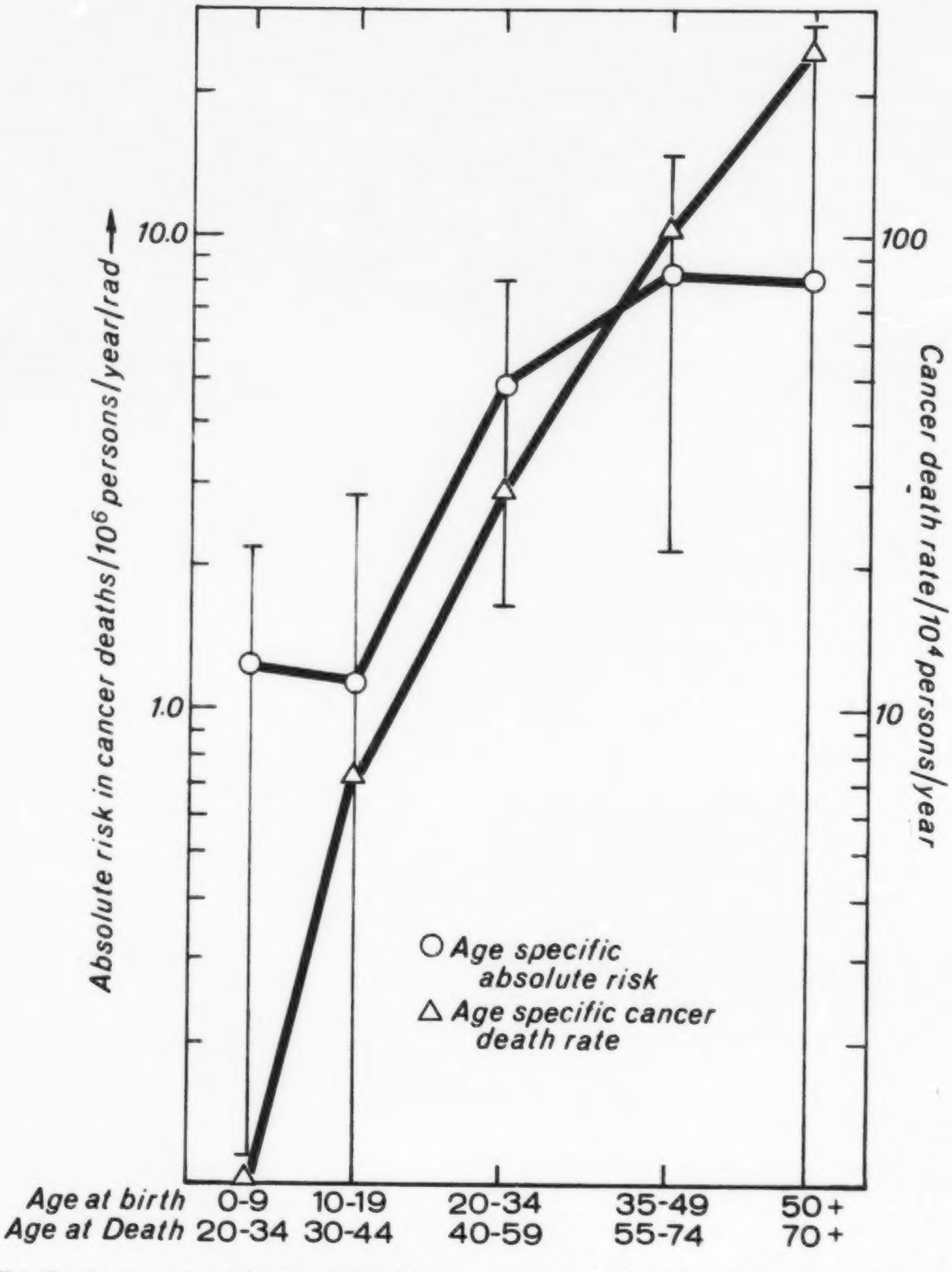

Figure III-2. The absolute risk of induction of all malignancies (except leukemia) in the A-bomb survivors versus age ATB. The data are for both cities and sexes combined, for deaths from 1960 to 1970 and no neutron RBE correction has been applied. The age specific death rate has been taken from the death rate in the 0-9 rad control group.

(ii) Irradiation at all subsequent times: a latency period of 2-3 years followed by a plateau length of 20-30 years for leukemia development, and for all other malignancies a latency period of 10 to 15 years (depending on the type of cancer) followed by a plateau region of between 20 years and the remaining lifetime of the individual.

The crucial difference in terms of predicting the annual excess cancer deaths between these estimates and those used by Gofman et al. (*20*) is the length of the plateau region following exposure *in utero*. For example, extension of the plateau region after irradiation *in utero* from 10 years to lifetime adds an additional 11,500 cancer deaths to the relative risk model of evaluating the effect of a continual exposure of 0.1 rem/year to the U. S. population. The reasons for the choice of a 10-year plateau region following *in utero* exposure have been discussed previously (II A-2).

The conclusion, therefore, is that the figures generated by Gofman et al. (*20*) are overestimates: The reasons for their overestimates are:

(i) An overestimation of the relative risk of solid tumor induction following irradiation of 0-9 year olds by a factor of 4-5, and by a factor of 10 for all other ages.

(ii) The unreasonable assumption of a lifelong plateau region following *in utero* irradiation.

No conclusion can be made at this time on the absolute versus relative risk dilemma. Should the absolute risk model be closer to reality, no numbers greater than approximately 3,000 extra cancer deaths from exposure of the U. S. population to 0.1 rem/year could be obtained given the present risk estimates, regardless of the lengths of any of the plateau regions for cancers other than leukemia.

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Appendix IV. Calculation of Confidence Limits for Risk Estimates

There are two classes of risk estimates:

1) Those based on comparison of the experience of a radiated group with expectation derived from national vital statistics or from other sources which are, in contrast with the data for the irradiated group, essentially constants, free from sampling variability.
2) Those based on the comparison of the experience of a radiated group with that of an unirradiated group. In this case the data for the comparison group must also be considered as subject to sampling fluctuation.

Class 1

For the irradiated group, let

x = number of deaths
P = number of person-years
D = average radiation dose

and let R be a population death rate appropriate for comparison, that is, standardized to the irradiated group for age, sex, and epoch. Then:

$$\text{Relative risk} = \frac{x}{P \cdot R}$$

$$\text{Doubling dose} = D \Big/ \left(\frac{x}{P \cdot R} - 1 \right) \quad (\text{if } > 0)$$

$$\text{Absolute risk} = (x - P \cdot R) / (D \cdot P) \times 10^6 \quad (\text{if } > 0)$$

In each of the above expressions, x is the only stochastic variable of interest. If upper and lower confidence limits for the true value of x can be found and substituted into these expressions, then the results will be confidence limits on the expressions.

Confidence limits for x are derived by considering x to be a realization of a Poisson variable, for which confidence limits on the mean can easily be obtained.

Class 2

In the unirradiated comparison group let:

y = number of deaths
Q = number of person-years

while notation for the irradiated group remains as before. Then:

$$\text{RR} = \text{Relative Risk} = \frac{x}{P} \Big/ \frac{y}{Q}$$

$$\text{DD} = \text{Doubling Dose} = D \Big/ \left(\frac{x}{P} \Big/ \frac{y}{Q} - 1 \right) \quad (\text{if} > 0)$$

$$\text{AR} = \text{Absolute Risk} = \left(x - \frac{P \cdot y}{Q} \right) \Big/ D \cdot P \times 10^6 \, (\text{if} > 0)$$

In the expressions for relative risk and for doubling dose, the stochastic elements enter only as the ratio x/y; while in the expression for absolute risk the stochastic term is $\frac{x}{P} - \frac{y}{Q}$, which can be seen writing the absolute risk expression as:

$$\left(\frac{x}{P} - \frac{y}{Q} \right) \Big/ D \cdot 10^6$$

We suppose x and y are independently distributed as Poisson variables with unknown mean values $\overline{X}$ and $\overline{Y}$. Then the joint distribution of x and y is:

$$\frac{\exp(-X - Y)}{x! \cdot y!} X^x \cdot Y^y$$

We impose the condition that $x + y$ be constant and, summing the corresponding probabilities, obtain:

$$\frac{\exp(-X - Y)\ (X + Y)^{x + y}}{(x + y)!}$$

as the total probability of $x + y$. Whence,

$$\left(\frac{x + y}{x}\right)\ \left(\frac{X}{X + Y}\right)^{x} \cdot \left(\frac{Y}{X + Y}\right)^{y}$$

is the conditional probability of x and y, on the condition that $x + y$ is constant. This is a binomial distribution with parameters $(x + y)$ and $X/(X + Y)$.

Let:

$p = X\Big/\left(X + Y\right)$, so that

$X/Y = P/(1 - p)$.

We obtain binomial confidence limits on p and this leads immediately to corresponding limits on the ratio X/Y, which in turn leads to limits on the relative risk and doubling dose.

As to the absolute risk, the true value is:

$$AR = \left(\frac{X}{P} - \frac{Y}{Q}\right)\Big/ D \times 10^{6}$$

and we can rewrite this as:

$$AR = \left(\frac{RR - 1}{RR \cdot P + Q}\right) \times \frac{(X + Y)}{D} \times 10^{6}$$

Confidence limits for the left-hand factor can be obtained easily from the previously obtained limits on RR and D is, of course, a known constant. The factor $X + Y$, the expected number of cases in the combined control and test group is, however, unknown. We obtain approximate limits by substituting the observed total number of cases, $x + y$, for the unknown expected total.

Appendix V. Radiation Dosimetry of Heavily Irradiated Sites in Patients Treated for Ankylosing Spondylitis

A. Introduction

The problem of radiation dose to the stomach and to the bronchus in patients treated with radiation for ankylosing spondylitis (*1*) centers on three main considerations: The position of the critical organ or tissue during treatment, the relationship of these structures to the irradiated fields and to depth dose data, and the frequency of radiation treatments received by the thoracic and lumbar spine. These values are important in the risk estimate for radiation-induced carcinoma of the stomach and carcinoma of the bronchus, and subsequently in the estimate of risk for cancers in heavily irradiated sites in these patients treated for ankylosing spondylitis.

B. Stomach

The stomach is obliquely placed in the left upper abdominal cavity; when the patient is prone, the fundus is posterior to the liver, and often adjacent laterally and sometimes posteriorly to the lower thoracic and upper lumbar vertebral bodies. The stomach may be of an asthenic, hyposthenic, sthenic or hypersthenic type, depending on the person's habitus (Figure V-1). The body of the stomach overlies the vertebral bodies to an appreciable degree only in the hypersthenic type. In the sthenic type, the pylorus overlies the vertebral bodies of the lumbar spine, and not the lower vertebral bodies of the thoracic spine. In hyposthenic and asthenic males, the pylorus may be deep in the pelvis; here, the stomach will frequently cross the midline and, thus, the vertebral bodies of the lumbar-5-sacral-1 level. Here, the lesser curvature of the body and fundus of the stomach runs in the paravertebral gutter, laterally adjacent to or posterior to the lumbar vertebral bodies (Figure V-1).

When thin patients lie in the prone position, the stomach and the duodenum press against the vertebral bodies; the gastrointestinal structures spread transversely, and surround the vertebral bodies laterally and anteriorly.

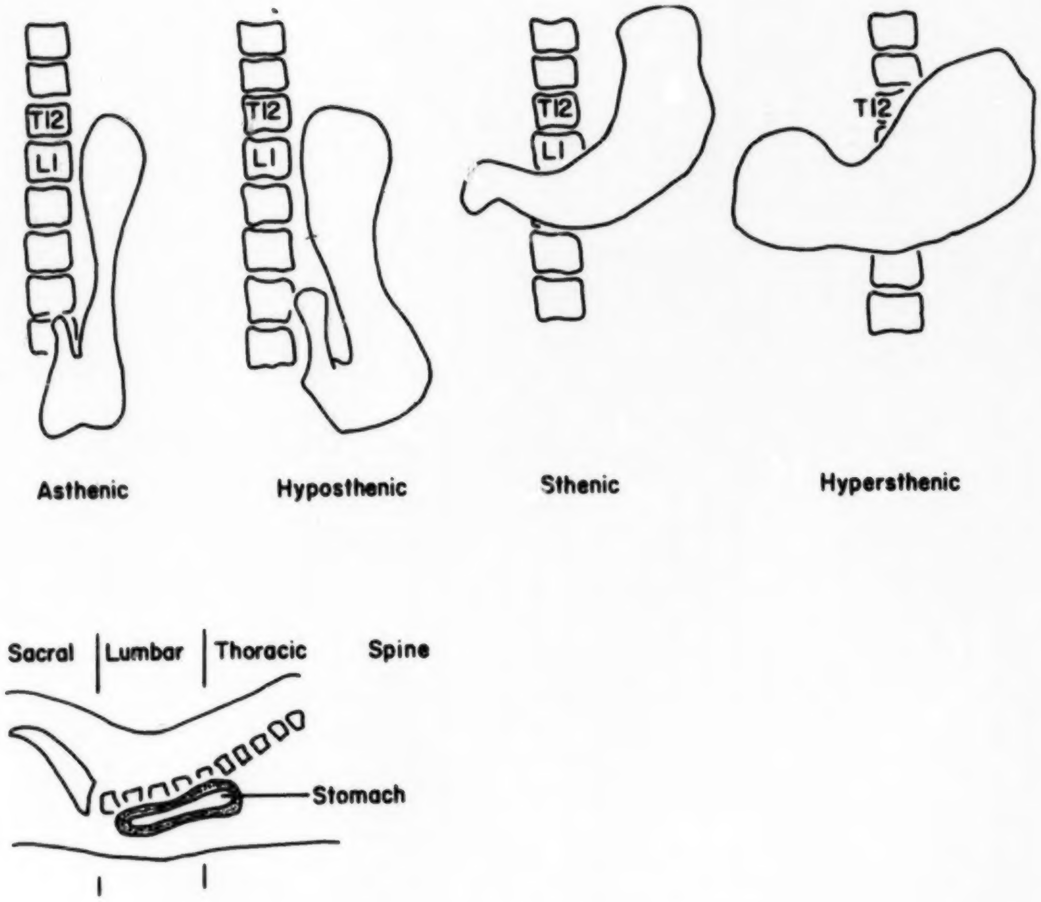
T12
L1
Asthenic
Hyposthenic
Sthenic
Hypersthenic
Sacral
Lumbar
Thoracic
Spine
Stomach

Figure V-1 Relative position of stomach and lumbar vertebral bodies.

On radiographic and fluoroscopic examination in which a barium meal is used, a pressure filling defect is observed. The variation in the anteroposterior thickness of the abdomen between the erect and prone positions may be great; the change in diameter is usually 3 to 5 cm in patients with average build, less in thin patients, and considerably more in obese patients.

The range for the anteroposterior diameter for most patients lying in the prone position is between 17 and 26 cm. In cadavers, fixed in the supine position, transverse sections at the level of the thoracic-12 vertebral body demonstrate the stomach to be lateral to and slightly anterior to the vertebral body (Figure V-2). If the mean thickness is approximately 21 cm, the midpoint of the relevant vertebral body from the surface of the back is 7.5 cm. The stomach will lie between 4.5 and 12 cm from the surface of the back, i.e., part of the fundus of the stomach will lie more posterior than the vertebral body.

Most frequently, the stomach lies below the level of the thoracic-11 vertebral body; it is therefore adjacent to the lumbar spine, not the thoracic (dorsal) spine. The lumbar spine is convex towards the anterior aspect of the trunk. In most patients, particularly in thin individuals in the prone position, the distance between the vertebral bodies and the anterior abdominal wall is less than, or at most equal to, the distance between the vertebral bodies and the posterior skin surface of the trunk. In such cases, the midpoint of the vertebral bodies may be 10 cm from the dorsal skin surface, and the stomach may lie from 6 cm to 16 cm from the dorsal surface of the trunk. The thoracic spine on the other hand is mildly convex towards the posterior aspect of the trunk. The rib cage prevents compression of the upper abdomen when the patient is prone, but the stomach may move upwards 4 to 8 cm, according to the patient's habitus. Here, the stomach will spread transversely with a comparable decrease in its length, and more of the gastric structure will be closer to the vertebral bodies of the lower thoracic spine.

The important conclusions are as follows: (a) The stomach is much more closely related to the lumbar spine than to the thoracic spine. (b) In thin patients in the prone position, the stomach is lateral and slightly anterior to the lumbar spine. Frequently, the fundus may be posterior to the midpoint of the lumbar vertebral bodies. (c) The radiation dose received by some portions of the stomach would be very little less than the closest vertebral body. (d) Depth-dose data derived from water and tissue-equivalent phantoms would not necessarily apply directly to each patient, and appropriate modifications would be necessary for the extent of anatomic variation in each individual patient.

In view of these anatomic observations, the calculations of Dolphin and Eve (*2*) must be revised; they underestimate the doses to heavily irradiated tissues. The stomach mucosa received a much higher dose relative to the adjacent vertebral bodies than estimated by Dolphin and Eve (*2*). Not all patients treated were included in their estimate, many more received exposure to the lumbar spine. Their estimate of mean dose to the vertebral bodies was based on the thoracic spine irradiation field, but should include the lumbar spine fields. Only one radiotherapeutic technique was used in their determinations, whereas a variety of techniques, filtration and field sizes was used in clinical practice.

From data of Court Brown and Doll (*1*), the mean radiation dose to the thoracic spine of treated patients determined as mean exposure to the bone marrow throughout the entire skeleton and as the maximum exposure at a point in the spinal marrow, was approximately 880 R. Based on depth-dose data for various orthovoltage and certain higher energy machines (*3*) the range of fall-off of dose with increasing depth was about 50% at 10 cm to 15 cm from the posterior skin surface of the trunk. When the lower thoracic spine was treated with field sizes greater than 8 to 10 cm in diameter the portion of the fundus of the stomach exposed would receive approximately the same dose as the lateral part of the adjacent vertebral body. In the orthovoltage range, this dose would fall from about 44% at 10 cm to 26% at 15 cm; in the supravoltage range, the decrease would be from 55% to 45%, respectively. Thus, the dose received by the mucosa of the exposed stomach when the patient was prone was approximately 40% to 50% of that of the vertebral body. More appropriate calculations, based on the radiotherapy dosimetry, would indicate a dose of greater than 250 R, and possibly 500 R. In this

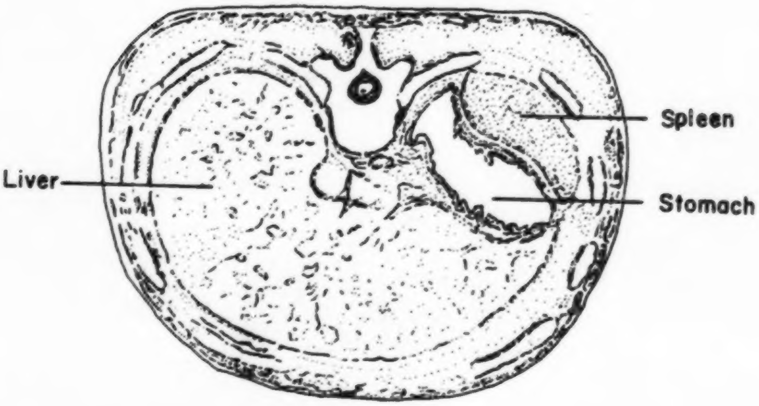
Spleen
Liver
Stomach
Transverse Section of Cadaver
at Thoracic - 12

Figure V-2. Transverse section of cadaver at thoracic-12 vertebra

489-797 O - 72 - 14

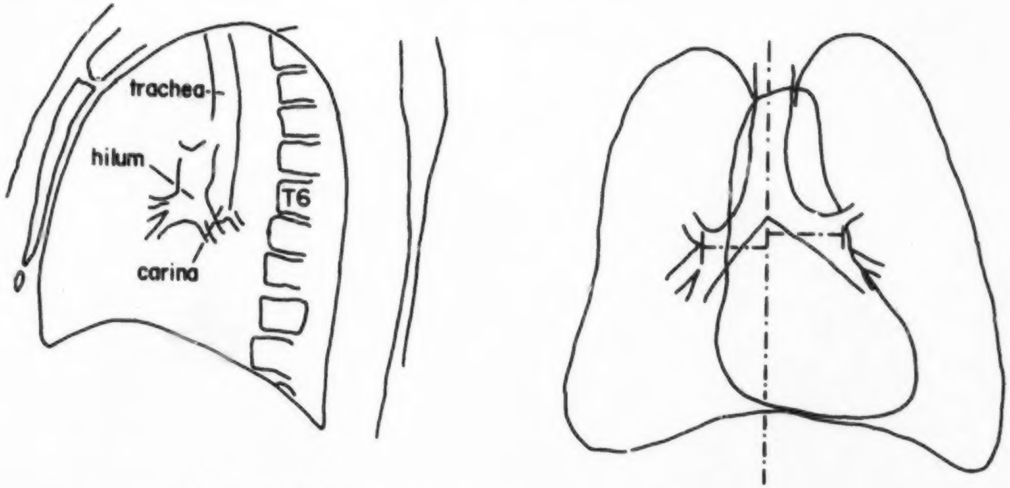
trachea
hilum
carina
T6

Figure V-3. Relative position of trachea to thoracic-7 vertebral body

report, the mean dose to the stomach in this series has been taken as 250-500 rads.

c. Lung

The bifurcation of the trachea at the carina in the adult is at the level of the thoracic-6 vertebral body, the main stem bronchi at approximately the thoracic-7 vertebral body, and the secondary bronchi at approximately the thoracic-7-thoracic-8 vertebral bodies (Figure V-3) (*4*). The mean width for the right and left hili is approximately 5.5 cm (over-all 11.0 cm) and over 85% of average persons demonstrate little difference, less than 1 cm, between the width of the two hili. The carina and hili lie in the mid-mediastinum. In general, the posteroanterior thickness for most patients in the prone position is between 25 and 35 cm. If the mean is 30 cm, the midpoint of the thoracic-7 vertebral body from the skin surface of the back is approximately 9 cm, and the carina and mainstem bronchi are approximately 15 cm. The thoracic spine is mildly convex towards the posterior aspect of the trunk. The rib cage prevents compression of the chest when the patient is in the prone position during radiotherapy.

The important conclusions are as follows: (a) In general, radiotherapy fields to the thoracic spine of patients with ankylosing spondylitis were approximately 10 cm. wide and 10 to 30 cm long (*1*). Divergence of the orthovoltage beam would readily include the carina, the mainstem bronchi, and the secondary bronchi in all patients. (b) In most patients, these structures are approximately 6 cm anterior to the vertebral bodies of the thoracic (dorsal) spine. Therefore, the bronchial mucosa received a relatively high dose in relation to the vertebral bodies. (c) Probably all patients with ankylosing spondylitis who received thoracic spine irradiation during treatment also received bronchial irradiation.

Based on depth-dose for various orthovoltage and some higher energy machines (*3*) the range of fall-off of dose with increasing depth is approximately 50% at 9 cm to 15 cm from the posterior skin surface of the trunk. In the orthovoltage range, this decrease is approximately 49% at 10 cm to 26% at 15 cm; in the supravoltage range, it is from 58% to 35%. Thus, the dose received by the bronchial mucosal epithelium, when the patient was prone during treatment, would be at least 40% to 50% of the dose to the closest thoracic vertebral body.

If it is assumed that the mean dose to the thoracic vertebral bodies was 880 R, that all patients received full radiation exposure to the critical bronchial structures, and that the dose to the bronchus ranged from 40% to 50% of the dose to the thoracic spine vertebral bodies, then the dose to the bronchus in these patients would be approximately 400 R. Thus, the calculations of Dolphin and Marley (*5*) are underestimates of the dose to the lung, possibly by a factor of 5, and should be revised to take into account the proper therapeutic radiation dosimetry. The figure of 400 rads has been used in this report to calculate the risk estimate for lung cancer from this series.

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Appendix VI: Definitions and Notes to Accompany Reference Tables Summarizing Quantitative Data on Carcinogenic Effects of Ionizing Radiation

The following notes and definitions are keyed to the numbered columns of the standard table format:

1. Study population - Each experience used here to estimate the risk of cancer attributable to exposure to ionizing radiation is briefly characterized as to reason for radiation or status at irradiation, geographic source if important, and calendar period of irradiation.

Hiroshima (H) and Nagasaki (N) A-bomb survivors are sometimes shown separately.

2. *Reference* - The bibliographic references from which the information on risk is drawn, keyed to the bibliography of the specific section. When additional information, or an assumption, is used in making the estimates, the additional source or the rationale is given in a footnote to the table.
3. *Type of Radiation* - Type of radiation is coded as follows:

α	Alpha
β	Beta
γ	Gamma
n	Neutron
x	X ray

4. Duration of radiation exposure - The total length of time over which radiation was received, not necessarily continuously. This will range from less than 10 seconds (<10″) for A-bomb survivors to years for some forms of intermittent radiotherapy. Duration may be shown merely as minutes (min), or as minutes to day, etc., or with the abbreviations wk (week), mo (month), and yr (year) being used.

5.-6. Reported duration of follow-up (years) - This is the length of time patients were followed up, with the *range* being the interval from the shortest to the longest period of follow-up when subjects are arrayed as to their individual years of follow-up. Time is usually counted from radiation exposure. In the 1965 report on ankylosing spondylitis patients it is indicated that the follow-up period ranges, essentially, from 5 to 27 years after radiation. The arithmetic mean of the frequency distribution of follow-up intervals is shown as the mean, and is the same as the range for A-bomb survivors.

7. *Period after irradiation on which risk estimates are based (years)* - Here time (t) is always measured from initial (?) radiation exposure as t_o, and for A-bomb survivors whose follow-up began 1 October 1950 and ended 31 December 1970 the interval is given as 6th-25th year and is about 20 years in length. The interval for risk calculation need not be the reported interval of observation, however, as when a period of latency is excluded. For example, in Hempelmann's follow-up on thymus irradiation (high-risk), duration of follow-up ranges from 17 to 32 years, but the risk of thyroid cancer is calculated for the interval 6-32 because the minimum latent period was estimated at five years in that study. Similarly, in tables on the risk of all cancer other than leukemia among A-bomb survivors, a latent period of 15 years is used, and data taken for 1960-1970 only.

8. *Number of subjects* - This is the number on which risk estimates are actually based. If only subjects aged 0-9 at exposure are used in the risk estimate, for example, only the number aged 0-9 at exposure is shown.

In prospective, or cohort, studies the irradiated subjects (N) are followed to define the subset of subsequent deaths from cancer, and it is N that is tabled here. In retrospective studies, where cancer cases and controls are studied to define the subsets with, and without, prior radiation, numbers of cases are not shown in the tables, but equivalent details are given in a special footnote to the table.

9. *Number of person-years* - This is the number of person-years at risk. This number is the denominator for absolute risk estimates. That is, the attributable incidence, I, may be found as

$$I = \frac{\text{Cases attributed to radiation}}{\text{Person-years at risk}}$$

which in these tables is expressed as cases/10^6/year/rem.

For retrospective studies the concept of person-years at risk does not apply, and no entry is made in this column.

10.-11. *Dose (rads)* - In most publications dose is given in rads. However, radiations of different quality or linear energy transfer (LET) may be of different relative biological effectiveness (RBE), and in this report risk estimates are given in rems insofar as possible, with the dose in rads multiplied by the RBE factor. The latter is obtained for a specified form of radiation as the ratio of the dose (in rads) of high energy x or gamma radiation required to produce a given level of biological effect, to the dose (in rads) of the specified form of radiation required to produce the same effect. Thus the RBE of x or gamma radiation is taken as 1. The rem dose is not shown explicitly in the tables, but is either equivalent to the dose in rads or may be found as the dose in rads × an RBE (column 17) if the dose in rads refers to a single type of radiation. Such is not the case for Hiroshima and Nagasaki where the total dose consisted of gamma and neutron radiation, the components of which are in these tables weighted 1:1 for RBE (neutrons) of 1, and 1:5 for RBE (neutrons) of 5.

An approximate range (column 10) and the arithmetic mean (column 11) are given separately, in recognition of the frequently important variation in individual dose. The range is the *external* dose.

The mean dose shown in column 11 is usually the relevant *tissue* dose but for the A-bomb survivors it is the whole-body, free field, or "air," dose. Attenuation factors for atomic bomb survivors have not been published, and hence no effort is made here to provide tissue doses, which might be 60 to 75 percent of the dose given in rads, depending on the tissue and the proportions of neutron and gamma radiation. For the ankylosing spondylitis patients the mean dose to the marrow of the spine, given as 880 rads, is here converted to a mean (whole body) marrow dose of 372 rads on the assumption that 42.3 percent of the entire marrow was irradiated. In the table on lung cancer, the reestimated average tissue dose to the lung of patients treated for ankylosing spondylitis is 400 rads, and for the stomach it is 250 to 500 rads (see App. *2.5*).

12 -13. Age at irradiation (years) - Both the range and the arithmetic mean are shown. A major distinction is made in these tables between A-bomb survivors under 10 at the time of the bomb and those aged 10 or more because of the greater relative sensitivity of the younger victims. Fetal ages at exposure are shown as 0, with no attempt to distinguish among the trimesters of gestation. In the pelvimetry series 87-89 percent were irradiated in the third trimester, in the A-bomb survivors, 27 percent.

14. *Sex* - Sex is coded as M (male) or F (female).

15. *Nature of control* - Since the risk that is sought in these tables is relative to a norm, or is the excess above that norm attributable to radiation, a normal basis of expectation is required. This is an intrinsic control (low-dose, 0-9 rads) group among the A-bomb survivors, or a calculation based on the vital statistics of the country or other jurisdiction where the experience took place. Most of the A-bomb survivors in the 0-9 rads range had 0 rads; their mean is estimated at 1.4 rads. When national mortality or incidence statistics are used as the basis of expectation, the name of the country is shown, in abbreviated form. Other geographic abbreviations are N. Y. (New York State), Ariz. (Arizona), Colo. (Colorado), N. Mex. (New Mexico). Other intrinsic controls are "sibs," siblings of treated cases, and "untreated" patients with the same disease but not treated by radiation.

    In retrospective studies the controls are defined differently from the above, which applies to prospective studies, and the information is shown, not in column 15, but in a special footnote to the table.

16. *Relative risk (O/E)* - For the period defined in column 7, the relative risk (RR) is expressed as observed (0) cases/expected (E) cases, where the expected cases represent the normal expectation estimated from the group defined in column 15. Thus, if U. K. mortality statistics were used to calculate expected deaths in the irradiated group this was often done by multiplying the person-years at risk for each sex and age

group, and calendar period by the corresponding U. K. mortality rates for the cancer of interest and summing the products. In this calculation the RR is equivalent to the standardized mortality ratio (SMR). In the case of the A-bomb survivors a calculation of this sort was done for each of several dose-groups, including the 0-9 rads group, and the corresponding SMR's were manipulated to produce the tabled value of E. Thus, for example, the SMR's for leukemia in subjects 0-9 ATB are as follows:

	0-9 Rads	10+ Rads
Observed deaths	7	19
Japanese expectation	4.572	1.909
SMR	1.531	9.953

Then E for 10+ rads = 1.909 x 1.531 = 2.93, and

O/E for 10+ rads = 19/2.93 = 6.50

In this case the ratio O/E is also the ratio of the two SMR's, i.e., 9.953/1.531 = 6.50.

The foregoing methods apply to prospective, or cohort, studies, but not to retrospective case/control studies. There is one such in the table on leukemia following exposure *in utero* or before age 10. In this study the data may be arranged as follows:

	In utero radiation	No in utero radiation	Total
Cases (leukemias)	a	b	a+b
Controls	c	d	c+d
Total	a+c	b+d	a+b+c+d

Then the relative risk is, approximately, ad/bc.[1]

17. *RBE* - Relative biological effectiveness (RBE) is defined above under columns 10-11, dose. In the sections on bone cancer and on lung cancer the RBE for alpha radiation is taken as 10 in calculating increase in risk per rem. In the tables on A-bomb survivors two calculations are routinely made, the RBE for neutrons being taken first as 1 and again as 5.
18. *Percent Increase in Relative Risk per Rem* - The percentage increase in relative risk (RR) is, of course

$$100 \times (\text{RR-1}), \text{ or } 100 \times (\text{Column 16-1}).$$

Then the percentage increase *per rem* is found as

$$\frac{100 \times (\text{RR-1})}{\text{Mean dose expressed in rem}}.$$

For x- and γ-radiation, and for neutron radiation with RBE = 1, this will be

$$\frac{100 \times (\text{Column 16-1})}{\text{Column 11}}.$$

For α-radiation this will be

$$\frac{100 \times (\text{Column 16-1})}{10 \times \text{Column 11}}.$$

For the A-bomb experience the entry in Column 11 is a mixture of α and neutron radiation, and the details of each would have to be tabled separately in order to illustrate the calculation at RBE = 5. If a mean dose (column 11) for the two cities were, for example, 69 rads made up of 10 rads of neutron radiation and 59 of gamma, then the calculation in column 18 would be

$$\frac{100\,(\text{Column 16-1})}{59 + 5 \times 10}.$$

The doubling dose is not used here (cf. pp. 99) but may be found from column 18 as

$$\text{doubling dose} = \frac{100}{\text{Column 18}}$$

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19-20. *Absolute Risk, Deaths or Cases/10⁶/Year/Rem* - This is the absolute risk attributable to radiation, i.e., the excess above normal expectation, and represents the slope of a linear dose-response curve giving the control incidence (or mortality rate) at zero dose. Three values are given: the best (or mean) estimate calculated from the data; a lower 90 percent limit on this estimate; and an upper 90 percent limit on it. These two limits define an 80 percent confidence interval. For prospective (cohort) studies the best estimate is found, for x-, α-, and n- radiation of RBE = 1, as

$$\frac{\text{O-E} \times 10^6}{\text{Column 9} \times \text{Column 11}}$$

In retrospective studies, where person-years are not available, the best estimate is found by multiplying the proportionate increase in risk per rem by the appropriate estimate of natural incidence or mortality, i.e.,

$$\frac{\text{Column 18}}{100} \times \text{natural rate.}$$

In Table a-7 (**page 117**), for example, the best estimate of 27 for the U. K. *in utero* study of Stewart et al. is found as 0.79 x the rate of 35 leukemia deaths per million/yr at ages 0-9 in U.K.

The calculation of confidence limits is described in Appendix IV. For the retrospective study (Table a-7, **page 117**) the method developed by Woolf[1] and modified by Haldane[2] was used.

21. *Footnotes or other comment* - Here will be found references to footnotes a, b, etc. to the particular table and other comments relating to the source-material or the calculation, e.g., adequacy of the dosimetry. Most series provide data on mortality; the exceptions are coded here as "morbidity."

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APPENDICES

Appendix A.

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Appendix B.

GLOSSARY

ABCC: Atomic Bomb Casualty Commission

Absolute risk: Product of assumed relative risk times the total population at risk. The number of cases that will result from exposure of a given population.

Absorption coefficient: Fractional decrease in the intensity of a beam of x or gamma radiation per unit thickness (linear absorption coefficient), per unit mass (mass absorption coefficient), or per atom (atomic absorption coefficient) of absorber, due to deposition of energy in the absorber. The total absorption coefficient is the sum of individual energy absorption processes (Compton effect, photoelectric effect, and pair production).

Accelerator (particle accelerator): A device for imparting large kinetic energy to electrically charged particles such as electrons, protons, deuterons and helium ions. Common types of particle accelerators are direct voltage accelerators, cyclotrons, etatrons, and linear accelerators.

Alpha particle: A charged particle emitted from the nucleus of an atom having a mass and charge equal in magnitude to a helium nucleus: i.e., two protons and two neutrons.

Angstrom unit: One angstrom unit equals 10^{-8} cm (Symbol: A).

Anion: Negatively charged ion.

Atomic mass: The mass of a neutral atom of a nuclide, usually expressed in terms of "atomic mass units." The "atomic mass unit" is one-twelfth the mass of one neutral atom of carbon-12; equivalent to 1 6604 X 10^{-24} g Symbol: u).

Attenuation: The process by which a beam of radiation is reduced in intensity when passing through some material. It is the combination of absorption and scattering processes and leads to a decrease in flux density of the beam when projected through matter.

Average life (mean life): The average of the individual lives of all the atoms of a particular radioactive substance. It is 1.443 times the radioactive half-life.

BEAR Committee: Advisory Committee on the Biological Effects of Atomic Radiation (Precursor of the BEIR Committee).

BEIR Committee: Advisory Committee on the Biological Effects of Ionizing Radiation.

Beta particle: Charged particle emitted from the nucleus of an atom, with a mass and charge equal in magnitude to that of the electron.

Bone seeker: Any compound or ion which migrates in the body preferentially into bone.

Bremsstrahlung: Secondary photon radiation produced by deceleration of charged particles passing through matter.

Carrier: A quantity of non-radioactive or non-labeled material of the same chemical composition as its corresponding radioactive or labeled counterpart. When mixed with the corresponding radioactive labeled material, so as to form a chemically inseparable mixture, the carrier permits chemical (and some physical) manipulation of the mixture with less label or radioactivity loss than would be true for the undiluted label or radioactivity.

Cation: Positively charged ion.

Chamber, ionization: An instrument designed to measure a quantity of ionizing radiation in terms of the charge of electricity associated with ions produced within a defined volume.

Curie: The special unit of activity. One curie equals 3,700 × 10^{10} nuclear transformations per second. (Abbr. Ci.) Common fractions are:

Megacurie: One million curies (Abbr. MCi)
Microcurie: One millionth ofa curie (3.7 × 10^4 disintegrations per second. Abbr. μCi)
Millicurie: One-thousandth of a curie (3.7 × 10^7 disintegrations per second. Abbr. mCi.)
Nanocurie: One-billionth of a curie (Abbr. nCi)
Picocurie: One-millionth of a microcurie (3.7 × 10^{-2}) disintegrations per second. (Abbr. pCi)

Daughter: Synonym for decay product.

Decay product: A nuclide resulting from the radioactive disintegration of a radionuclide, formed either directly or as the result of successive transformations in a radioactive series. A decay product may be either radioactive or stable.

Decay, radioactive: Disintegration of the nucleus of an unstable nuclide by spontaneous emission of charged particles and/or photons.

Dose: A general form denoting the quantity of radiation or energy absorbed. For special purposes it must be appropriately qualified. If unqualified, it refers to absorbed dose.

Absorbed dose: The energy imparted to matter by ionizing radiation per unit mass of irradiated material at the place of interest. The unit of absorbed dose is the rad. One rad = 100 ergs per gram, or 0.01 J/pg.
Cumulative dose: Total dose resulting from repeated exposure to radiation.

Dose equivalent (DE): Quantity that expresses all radiations on a common scale for calculating the effective absorbed dose. It is defined as the product of the absorbed dose in rads and certain modifying factors. The unit of DE is the rem.

Genetically significant dose (GSD): The gonad dose from medical exposure which, if received by every member of the population, would be expected to produce the same

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total genetic effect on the population as the sum of the individual doses actually received. The GSD can be expressed algebraically as:

$$GSD = \frac{\sum D_i N_i P_i}{\sum N_i P_i}$$

D_i = Average gonad dose to persons age i who received x-ray examinations

N_i = Number of persons in population of age i who receive x-ray examinations

Pi = Expected future number of children for person of age i

Ni = number of persons in population of age i.

In 1964 the GSD was computed to be 55 millirads per person per year, for the United States. An estimated 55% of the population were receiving x-rays at that time. Thus, the average dose to those receiving medical radiation could be computed to be approximately 80 millirads.

Maximum Permissible Dose Equivalent (MPD): The greatest dose equivalent that a person or specified part thereof shall be allowed to receive in a given period of time.

Median Lethal Dose (MLD): Dose of radiation required to kill, within a specified period, 50% of the individuals in a large group of animals or organisms. Also called LD_{50}.

Permissible Dose: The dose of radiation which may be received by an individual within a specified period with expectation of no significantly harmful result.

Threshold Dose: The minimum absorbed dose that will produce a detectable degree of any given effect.

Doubling Dose: The amount of radiation needed to double the natural incidence of a genetic or somatic anomaly.

Dose, Fractionation: A method of administering radiation, in which relatively small doses are given daily or at longer intervals.

Dose, Protraction: A method of administering radiation by delivering it continuously over a relatively long period at a low dose rate.

Dose rate: Absorbed dose delivered per unit time.

Electron Volt: A unit of energy equivalent to the energy gained by an electron in passing through a potential difference of one volt. Larger multiple units of the electron volt are frequently used: KeV for thousand or *kilo electron volts;* MeV for million or *mega electron volts.* (Abbr. eV, 1 eV = 1.6×10^{-12} erg.)

EPA: Environmental Protection Agency

Exposure: A measure of the ionization produced in air by x or gamma radiation. It is the sum of the electrical charges on all ions of one sign produced in air when all electrons liberated by photons in a volume element of air are completely stopped in air, divided by the mass of the air in the volume element. The special unit of exposure is the roentgen.

Acute exposure: Radiation exposure of short duration.

Chronic exposure: Radiation exposure of long duration by fractionation or protraction.

Fission, nuclear: A nuclear transformation characterized by the splitting of a nucleus into at least two other nuclei and the release of a relatively large amount of energy.

Fission products: Elements or compounds resulting from fission.

Fission yield: The percentage of fissions leading to a particular nuclide.

FRC: Federal Radiation Council

Fuel cycle: The sequence of steps, such as utilization, reprocessing, and refabrication, through which nuclear fuel passes.

Fusion, nuclear: Act of coalescing two or more atomic nuclei

Gamma ray: Short wavelength electromagnetic radiation of nuclear origin (range of energy from 10KeV to 9MeV) emitted from the nucleus.

Gram atomic weight: A mass in grams numerically equal to the atomic weight of an element.

Gram molecular weight (gram-mole): Mass in grams numercally equal to the molecular weight of a substance.

Gram-Rad: Unit of integral dose equal to 100 ergs.

Half-life, biological: The time required for the body to eliminate one-half of an administered dosage of any substance by regular processes of elimination. Approximately the same for both stable and radioactive isotopes of a particular element.

Half-life, effective: Time required for a radioactive element in an animal body to be diminished 50% as a result of the combined action of radioactive decay and biological elimination.

$$\text{Effective half-life} = \frac{\text{Biological half-life} \times \text{radioactive Half-life}}{\text{Biological half-life} + \text{Radioactive half-life}}$$

Half-life, radioactive: Time required for a radioactive substance to lose 50% of its activity by decay. Each radionuclide has a unique half-life.

ICRP: International Commission on Radiological Protection

ICRU: International Commission on Radiation Units and Measurements

Incidence: The rate of occurrence of a disease within a specified period of time; usually expressed in number of cases per million (10^6) per year.

Ion: Atomic particle, atom, or chemical radical bearing an electrical charge, either negative or positive.

Ion exchange: A chemical process involving reversible interchange of ions between a solution and a particular solid material such as an ion exchange resin consisting of a matrix of insoluble material interspersed with fixed ions of opposite charge.

Ionization: The process by which a neutral atom or molecule acquires a positive or negative charge.

Primary ionization: In collision theory; the ionization produced by the primary particles as contrasted to the "total ionization" which includes the "secondary ionization" produced by delta rays.

Secondary ionization: Ionization produced by delta rays.

Ionization density: Number of ion pairs per unit volume.

Ionization path (track): The trail of ion pairs produced by an ionizing radiation in its passage through matter.

Isotopes: Nuclides having the same number of protons in their nuclei, and hence the same atomic number, but differing in the number of neutrons, and therefore in the mass number. Almost identical chemical properties exist between isotopes of a particular element. The term should not be used as a synonym for nuclide.

Labeled compound: A compound consisting, in part, of labeled molecules. By observations of radioactivity or isotopic composition, this compound or its fragments may be followed through physical, chemical, or biological processes.

Latent period: The period or state of seeming inactivity between the time of exposure of tissue to an injurious agent and response

LD_{50} (radiation dose) (See: Dose, median lethal.

Linear energy transfer (LET): The average amount of energy lost per unit of particle spur-track length.

Low-LET: Radiation characteristic of electrons, x rays, and gamma rays

High-LET: Radiation characteristic of protons or fast neutrons

Average LET is specified to even out the effect of a particle that is slowing down near the end of its path and to allow for the fact that secondary particles from photon or fast-neutron beams are not all of the same energy.

AVERAGE LET VALUES

Particle	Mass amu	Charge	Energy (KeV)	Average LET (KeV/micron)	Tissue Penetration (microns)
Electron	0.00055	-1	1	12.3	.01
			10	2.3	1
			100	0.42	180
			1000	0.25	5000
Proton	1	+1	1 0 0	90	3
			2000	16	80
			5000	8	350
			10000	4	1400
Deuteron	2	+1	10000	6	700
			200000	1.0	190000
Alpha	4	+2	100	260	1
			5000	95	35
			200000	5	20000

Linear hypothesis: The assumption that a dose-effect curve derived from data in the high dose and high dose-rate ranges may be extrapolated through the low dose and low dose range to zero, implying that, theoretically, any amount of radiation will cause some damage.

Nam-rems: See person-rems.

Maximum credible accident: The worst accident in a reactor or nuclear energy installation that, by agreement, need be taken into account in deriving protective measures.

Medical exposure: Exposure to ionizing radition in the course of diagnostic or therapeutic procedures. As used in this report, the term includes:

1. Diagnostic radiology (e.g., x rays)
2. Exposure to radioisotopes in nuclear medicine (e.g., iodine-131 in thyroid treatment)
3. Therapeutic radiation (e.g., cobalt treatment for cancer)
4. Dental exposure

Micron: Unite of length equal to 10^{-6} meters. (symbol μ)

Morbidity: 1. The condition of being diseased.
2. The ratio of sick to well persons in a community.

NAS-NRC: National Academy of Sciences - National Research Council

NCRP: National Council on Radiation Protection and Measurements

Neoplasm: Any new and abnormal growth, such as a tumor. The term "neoplastic disease" refers to any disease which forms tumors, malignant or benign.

Nuclide: A species of atom characterized by the constitution of its nucleus. The nuclear constitution is specified by the number of protons (Z), number of neutrons (N), and energy content; or, alternatively, by the atomic number (Z), mass number $A = (N + Z)$, and atomic mass. To be regarded as a distinct nuclide, the atom must be capable of existing for a measurable time. Thus, nuclear isomers are separate nuclides, whereas promptly decaying excited nuclear states and unstable intermediates in nuclear reactions are not so considered.

Person-rems: The product of the average individual dose in a population times the number of individuals in the population. Syn: man-rems.

Plateau: A period of above-normal, relative uniform, incidence of morbidity or mortality in response to a given biological insult.

Prevalence: The number of cases of disease in existence at a certain time in a designated area.

Quality Factor (QF): The linear-energy-transfer-dependent factor by which absorbed doses are multiplied to obtain (for radiation protection purposes) a quantity that expresses — on a common scale for all ionizing radiations — the effectiveness of the absorbed dose.

Rad. The unit of absorbed dose equal to 0.01 J/kg in any medium.

Radiation: 1) The emission and propagation of energy through space or through a material medium in the form of waves; e.g., the emission and propagation of electromagnetic waves, or of sound and elastic waves. 2) The energy propagated through space or through a material medium as waves. The term radiation or radiant energy, when unqualified, usually refers to electromagnetic radiation. Such radiation is commonly classified by frequency: Hertzian, infrared, visible, ultraviolet, x ray, and gamma ray. 3) Corpuscular emissions, such as alpha and beta radiation, or rays of mixed or unknown type, as cosmic radiation.

Background radiation: Radiation arising from radioactive material other than the one directly under consideration. Background radiation due to cosmic rays and natural radioactivity is always present. There may also be background radiation due to the presence of radioactive substances in other parts of the building, in the building material itself, etc.

External radiation: Radiation from a source outside the body.

Internal radiation: Radiation from a source within the body (as a result of deposition of radionuclides in body tissue).

Ionizing radiation: Any electromagnetic or particulate radiation capable of producing ions, directly or indirectly, in its passage through matter.

Secondary radiation: Radiation resulting from absorption or other radiation in matter. It may be either electromagnetic or particulate.

Radioactivity: The property of certain nuclides of spontaneously emitting particles or gamma radiation or of emitting X radiation following orbital electron capture or of undergoing spontaneous fission.

Artificial radioactivity: Manmade radioactivity produced by particle bombardment or electromagnetic irradiation.

Natural radioactivity: The property of radioactivity exhibited by naturally occurring radionuclides.

Radiosensitivity: Relative susceptibility of cells, tissues, organs, organisms, or any living substance to the injurious action of radiation. Radiosensitivity and its antonym *radioresistance*, are currently used in a comparative sense, rather than in an absolute one.

Rate, recovery: The rate at which recovery takes place after radiation injury. It may proceed at different rates for different tissues. "Differential recovery rate": Among tissues recovering at different rates, those having slower rates will ultimately suffer greater damage from a series of successive irradiations. This differential effect is considered in fractionated radiation therapy if the neoplastic tissues have a slower recovery rate than surrounding normal structures.

Rays:

Alpha: Beams of helium nuclei (2 protons and 2 neutrons)

Beta: **Beams of electrons or positrons.**

Gamma: Beams of high-energy photons from radioactively decaying elements.

X: Beams of mixed lower energy photons.

Neutron: **Beams of neutrons.**

Proton: Beams of protons.

Reactor, breeder: A reactor which produces more fissile material than it consumes; i.e., has a conversion ratio greater than unity.

Reactor converter: A reactor which produces fissile atoms from fertile atoms, but has a conversion ratio less than one.

Reactor, nuclear: An apparatus in which nuclear fission may be sustained in a self-supporting chain reaction.

Relative Biological Effectiveness (RBE): The RBE is a factor used to compare the biological effectiveness of absorbed radiation doses (i.e., rads) due to different types of ionizing radiation; more specifically, it is the experimentally determined ratio of an absorbed dose of a radiation in question to the absorbed dose of a reference radiation required to produce an idential biological effect in a particular experimental organism or tissues. The RBE is the ratio of rem to rad. (If 1 rad of fast neutrons equalled in lethality **3.2 rads of 250 KVP x rays, the RBE of the fast neutrons would be 3.2).**

Relative risk: The ratio of the risk in those exposed to the risk to those not exposed (incidence in exposed population to incidence in control population).

Rem: A special unit of dose equivalent. The dose equivalent in rems is numerically equal to the absorbed dose in rads multiplied by the quality factor, the distribution factor, and any other necessary modifying factors. The *rem* represents that quantity of radiation that is equivalent—in biological damage of a specified sort—to 1 rad of 250 **KVP x rays. See note p. 86.**

Roentgen (R): The special unit of exposure. One roentgen equals 2.58 X 10^{-4}coulomb per kilogram of air.

Sickness, radiation: A self-limited syndrome characterized by nausea, vomiting, diarrhea, and psychic depression, following exposure to appreciable doses of ionizing radiation, particularly to the abdominal region. Its mechanism is unknown and there is no satisfactory remedy. It usually appears a few hours after irradiation and may subside within a day. It may be sufficiently severe to necessitate interrupting the treatment series or to incapacitate the patients.

Sigmoid curve: S-shaped curve, often characteristic, e.g., of a dose-effect curve in radiobiological studies.

Softness: A relative specification of the quality or penetrating power of **x rays**. In general, the longer the wave length the softer the radiation.

Specific activity: Total activity of a given nuclide per gram of a compound, element, or radioactive nuclide.

Target theory (Hit Theory): A theory explaining some biological effects of radiation on the basis that ionization, occurring in a discrete volume (the target) within the cell, directly causes a lesion which subsequently results in a physiological response to the damage at that location. One, two, or more "hits" (ionizing events within the target) may be necessary to elicit the response.

Threshold hypothesis: the assumption that no radiation injury occurs below a specified dose level.

UNSCEAR: United Nations Scientific Committee on the Effects of Atomic Radiation

Working Level (WL): Any combination of short-lived radon daughters in 1 liter of air that will result in the ultimate emission of 1.3 X 10^5 MeV of potential alpha energy.

Working Level Month (WLM): Inhalation of air with a concentration of 1 WL of radon daughters for 170 working hours results in an exposure of 1 WLM.

X rays: Penetrating electromagnetic radiations whose wave lengths are shorter than those of visible light. They are usually produced by bombarding a metallic target with fast electrons in a high vacuum. In nuclear reactions, it is customary to refer to photons originating in the nucleus as gamma rays, and those originating in the extranuclear part of the atom as X rays. These rays are sometimes called roentgen rays, after their discoverer, W. C. Roentgen.

Appendix C.

Record of Meetings

Chronology of Meetings of the Advisory Committee on the Biological Effects of Ionizing Radiations and its Subcommittees

1970-1972

March 25, 1970 September 23, 1970 January 19, 1971 May 27, 1971 October 7-8, 1971 December 9-10, 1971 June 1-2, 1972	Advisory Committee on the Biological Effects of Ionizing Radiations
December 1, 1970 February 8, 1971 May 6-7, 1971	Subcommittee on Effects on Growth and Development
November 30, 1970 February 16, 1971 September 2-3, 1971	Subcommittee on Environmental Effects
November 21, 1970 December 22, 1970 March 18, 1971 May 20, 1971 July 24, 1971 September 30, 1971 November 12-13, 1971 January 6, 1972	Subcommittee on Genetic Effects
November 23, 1970 January 18, 1971 March 29, 1971 May 26, 1971 July 15-16, 1971 September 8-10, 1971 November 11-12, 1971 December 8, 1971 January 10-12, 1972 March 2-3, 1972	Subcommittee on Somatic Effects
March 17, 1972	Subgroup Meeting (Somatic Effects)
July 17, 1972 September 14, 1971 October 9, 1971	*Ad Hoc* Committee (BEIR)
January 13, 1972	Joint Meeting: Subcommittee on Effects on Growth and Development; Subcommittee on Somatic Effects
January 14, 1972	Meeting of Subcommittee Chairmen

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